NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency [ID4036]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency [ID4036]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Merk Sharp & Dohme:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. AMMF

4. **External Assessment Report** prepared by KSR

5. **External Assessment Group response to factual accuracy check of EAR**

6. **Technical engagement response** from Merk Sharp & Dohme

7. **Technical engagement response & personal statement from experts:**
   a. Andrea Sheardown, patient expert – nominated by AMMF
   b. Helen Morement, patient expert – nominated by AMMF
   c. Kai-Keen Shiu, clinical expert – nominated by MSD

8. **External Assessment Group critique of company response to technical engagement** prepared by KSR
   a. EAG critique
   b. Additional scenario analyses
   c. Base-case fully incremental results without QALY weights

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 previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Document B

Company evidence submission

January 2023

File name	Version	Contains confidential information	Date
NICE ID4036 – pembrolizumab previously treated solid tumours dMMR MSI-H Document B [ACIC]	**1.0**	**Yes**	**17 January 2023**

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Abbreviations

Abbreviation	Definition
AE	Adverse events
AEOSI	Adverse event of special interest
AIC	Akaike information criterion
ASaT	All subjects as treated
BHM	Bayesian hierarchical model
BIC	Bayesian information criterion
CI	Confidence interval
CR	Complete response
CRC	Colorectal carcinoma
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
DCR	Duration of complete response
DIC	Deviance information criterion
dMMR	DNA mismatch repair deficient
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSU	Decision Support Unit
ECOG PS	Eastern Cooperative Oncology Group performance score
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
ESMO	European society of medical oncology
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
(m)FOLFIRI	(Modified) folinic acid, fluorouracil, irinotecan
(m)FOLFOX	(Modified) folinic acid, fluorouracil, oxaliplatin
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRC	Independent radiologist review committee
IHC	Immunohistochemistry
IPD	Individual patient data
ITC	Indirect treatment comparison
KM	Kaplan–Meier
LS	Lynch syndrome
LY	Life year
mAB	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
MSI-H	Microsatellite instability high
MSS	Microsatellite stable
NICE	National Institute for Health and Care Excellence
NCCN	National Comprehensive Cancer Network
ONS	Office for National Statistics
ORR	Objective response rate
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2

PFS	Progression-free survival
pMMR	Proficient mismatch repair
PR	Partial response
OS	Overall survival
Q3W	Once every three weeks
QALY	Quality-adjusted life year
RT	Radiotherapy
RECIST	Response evaluation criteria in solid tumours
SoC	Standard of care
TMB-H	Tumour mutation burden high
TPC	Treatment of physician's choice
TSD	Technical Support Document
TTD	Time to treatment discontinuation
VEGF	Vascular endothelial growth factor

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

Summary of the decision problem, technology, and clinical care pathway

- Pembrolizumab was approved by the MHRA on 16 May 2022 for treatment of the following MSI-H or dMMR tumours in adults with:
  - Unresectable or metastatic **colorectal cancer** after previous fluoropyrimidine-based combination therapy
  - Advanced or recurrent **endometrial carcinoma**, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation
  - Unresectable or metastatic **gastric**, **small intestine**, or **biliary cancer**, who have disease progression on or following at least one prior therapy
- The submission covers the technology's full marketing authorization for this indication. The relevant comparators for each of the tumour sites have been identified based on international guidelines and clinical expert consultation and are representative of the clinical practice in England
- Pembrolizumab is a humanized monoclonal antibody which binds to the programmed death-ligand 1 (PD-L1) receptor that is involved in the control of T-cell immune responses, thereby potentiating an immune response to tumour cells
- Microsatellite instability-high (MSI-H) is a form of genomic instability caused by mutations in the mismatch repair (MMR) genes responsible for repairing damaged or mismatched DNA in microsatellites during DNA replication, which may predispose to different type of cancers. MSI-H cancers can demonstrate highly upregulated expression of PD-1 and PD-L1 as well as other immune checkpoints ligands, thereby providing a scientific rationale for PD-1 blockade with pembrolizumab for the management of patients with MSI-H cancer
- For patients with tumours confirmed to be MSI-H/dMMR it is anticipated that pembrolizumab will be used as an alternative to chemotherapy for patients with advanced, previously treated colorectal, endometrial, gastric, small intestine and biliary cancers. Relevant chemotherapy comparators depend on the cancer type

- No equity or equality considerations are anticipated

B.1.1 Decision problem

The submission covers the technology's full marketing authorization 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 unresectable or metastatic MSI-H or dMMR colorectal cancer previously treated with fluoropyrimidine-based combination therapy. Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation. Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy.	Adults with unresectable or metastatic MSI-H or dMMR colorectal cancer previously treated with fluoropyrimidine-based combination therapy. Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation. Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy	In line with final NICE scope
Intervention	Pembrolizumab	Pembrolizumab	In line with final NICE scope
Comparator(s)	**For people with previously treated MSI-H or dMMR with unresectable or metastatic colorectal cancer:** • Established management without pembrolizumab • Nivolumab with ipilimumab	**For people with previously treated MSI-H or dMMR with unresectable or metastatic colorectal cancer:** • FOLFIRI/FOLFOX/FOLFOX4/ mFOLFOX6 (70% of eligible patients)	**For people with previously treated MSI-H or dMMR with unresectable or metastatic colorectal cancer:** Single-agent irinotecan and raltitrexed are not considered relevant comparators in this appraisal as clinical expert

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Single-agent irinotecan (after FOLFOX) • FOLFIRI (after either FOLFOX or CAPOX) • Raltitrexed (if 5-fluorouracil and folinic acid are not suitable) • Trifluridine-tipiracil **For people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer:** • Established management without pembrolizumab • Chemotherapy, including: - Carboplatin and paclitaxel - Paclitaxel monotherapy - Doxorubicin monotherapy - Carboplatin monotherapy • Hormone therapy (such as medroxyprogesterone acetate and megestrol) **For people with previously treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine, or biliary cancer**	• Trifluridine-tipiracil (30% of eligible patients **For people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer:** • Chemotherapy, including: - Paclitaxel, doxorubicin and carboplatin **For people with previously treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine and biliary cancer:** <u>Gastric cancer</u> • Paclitaxel • FOLFIRI <u>Small intestine cancer</u> • FOLFIRI/FOLFOX <u>Biliary cancer</u> • FOLFOX • FOLFIRI	opinion confirmed that they are not routinely used in clinical practice unless other treatments are contraindicated. Nivolumab with ipilimumab is not considered a relevant comparator in this appraisal. Given that nivolumab with ipilimumab cannot be used to treat patients who received any prior treatment with an anti-PD-1 antibody, and pembrolizumab is the standard of care for patients with untreated metastatic colorectal cancer with MSI-H or dMMR, nivolumab with ipilimumab will be the treatment of choice for a small subset of people who receive fluoropyrimidine-based combination chemotherapy in first-line when the MSI-H/MMR status is not yet confirmed or where the progression of the disease requires fast acting chemotherapy. Clinical expert opinion suggested that these patients will routinely receive nivolumab with ipilimumab unless there are comorbidities. In these instances, which are expected to occur in a small proportion of patients (subset of the subset)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Established management without pembrolizumab		pembrolizumab may be a suitable option.(1) **For people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer:** • Based on clinical expert consultation, standard of care is chemotherapy such as paclitaxel, doxorubicin and carboplatin.(1) • Hormone therapy is only used with palliative intent if all other treatment options are exhausted, or patients cannot tolerate further lines of chemotherapy which is not the proposed positioning for pembrolizumab. **For people with previously treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine and biliary cancer:** Established clinical management without pembrolizumab has been identified based on European

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			guidelines and clinical expert consultation. With regard to small intestine cancer, clinical experts identified FOLFOX/FOLFIRI as the treatment of choice but did not expect MSD to find any published evidence on efficacy.(1) This was confirmed in the systematic literature review which only identified evidence for nab-paclitaxel, which is used in the cost-effectiveness analysis.
Outcomes	• Overall survival • Progression free survival • Response rate • Duration of response • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression free survival • Response rate • Duration of response • Adverse effects of treatment • Health-related quality of life	N/A
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.	Cost-effectiveness of the treatments specified are expressed in terms of incremental cost per quality-adjusted life year. The economic analysis implements a lifetime time horizon for estimating clinical and cost-effectiveness.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Costs are included from an NHS and Personal Social Services perspective and use sources reflecting the current prices available to the NICE (with the exception of therapies available with a confidential discount).	
	The use of pembrolizumab for this indication is conditional on the presence of either MSI-H or dMMR classified tumours. The economic modelling should include the costs associated with diagnostic testing for MSI-H or dMMR in people with solid tumours who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introductionto-health-technology-evaluation).	Testing costs are not included in the base case analysis.	Previous appraisals and clinical opinion suggest testing is well established in colorectal and endometrial cancer and so for consistency testing costs are not included in the base-case. However, testing costs for the remaining tumour sites are explored in scenario analyses.
Subgroups to be considered	If the evidence allows the following subgroups will be	Cost-effectiveness analysis for each tumour site are provided.	No additional subgroup analysis was performed.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	considered: • Tumour site • Previous therapy		
Special considerations including issues related to equity or equality		No issues with equity or equality have been identified.	

B.1.2 Description of the technology being evaluated

Pembrolizumab (KEYTRUDA®, MSD) is a humanized monoclonal anti-programmed cell death-1 antibody, which binds to the programmed death-ligand 1 (PD-L1) receptor, thereby blocking its interaction with ligands PD-L1 and programmed death-ligand 2 (PD-L2).(2, 3) The programmed cell death protein (PD-1) receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. PD-L1 and PD-L2 are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Table 2 presents a description of pembrolizumab for the indication being appraised. The draft Summary of Product Characteristics (SmPC) and European Public Assessment report (EPAR) are presented in Appendix C.

Table 2 Technology being evaluated

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) is a monoclonal antibody (mAB) 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	Regulatory approval for pembrolizumab in the indication relevant to this appraisal has already been granted for GB (MHRA: PL GB 53095/0040) on 16 May 2022 and EU (EMEA/H/C/003820/II/0109)(4) on 25 April 2022.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings: • Treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy. KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with: • Advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;

	• Unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy. Pembrolizumab has already been approved by EMA and MHRA for the first-line treatment of adults with MSI-H or dMMR colorectal cancer. In addition, pembrolizumab, as monotherapy or in combination with other agents, is licenced for specific indications in: • Melanoma • Non-small cell lung cancer • Classical Hodgkin lymphoma • Urothelial carcinoma • Head and neck squamous cell carcinoma • Renal cell carcinoma • Oesophageal cancer • Triple-negative breast cancer (TNBC) • Endometrial carcinoma • Cervical cancer
Method of administration and dosage	Pembrolizumab as monotherapy 200 mg every 3 weeks (Q3W) or 400 mg 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 100 mg vial
Patient access scheme (if applicable)	A patient access scheme (PAS) is in place which makes pembrolizumab available to the NHS for a discount of [redacted]

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

B.1.3.1 Health condition

The population relevant for this submission is adults with DNA mismatch repair deficient (dMMR) / MSI-H (microsatellite instability high) tumours who have been previously treated for:

- unresectable or metastatic colorectal, gastric, small intestine, or biliary cancer,
- or advanced or recurrent endometrial cancer, who are not candidates for curative surgery or radiotherapy.

The DNA mismatch repair (MMR) system repairs damaged or mismatched DNA during DNA replication. Mutations in the MMR genes cause dysfunctional MMR proteins incapable of recognizing DNA mismatch in microsatellites, the coding regions of repetitive sequences with DNA. As a result, DNA damage fails to be repaired and may lead to the generation of non-functional protein. This form of genomic instability is called microsatellite instability (MSI).(5) Inactivation of the MMR gene can either be somatic (sporadic) or of germline origin (e.g. Lynch syndrome). Lynch syndrome (LS) is a hereditary disorder with an autosomal dominant transmission that primarily predisposes to colorectal and endometrial cancer, but is also associated with other malignancies, such as stomach, small bowel, and biliary tract cancers.(6, 7)

MMR or MSI status can be determined by examining either (1) protein expression by immunohistochemistry (IHC) of 4 MMR proteins (MLH1/MSH2/MSH6/PMS2) or (2) 3 to 5 tumour microsatellite loci by using a polymerase chain reaction (PCR) assay. In general, tumours are classified as MSI-H (including MMR deficient) when expression of at least 1 of 4 MMR proteins is not detectable by IHC, or when at least 2 allelic size shifts among 3 to 5 analysed microsatellite markers are detected by PCR.(8) Tumours that are not classified as MSI-H/dMMR are classified as microsatellite stable (MSS), or MMR proficient (pMMR).

MSI-H and dMMR cancers can demonstrate highly upregulated expression of PD-1 and PD-L1 as well as other immune checkpoints ligands, thereby providing a scientific rationale for PD-1 blockade with pembrolizumab for the management of patients with MSI-H cancer.(9) It has been demonstrated that the mismatch repair–deficient tumour microenvironment strongly expressed several immune checkpoint receptors and ligands, including PD-1 and PD-L1, which indicates that their active immune microenvironment is counterbalanced by immune inhibitory signals that resist tumour elimination.(10) Many studies have shown that PD-L1 expression is associated with superior response to an anti-PD-1 inhibitor such as pembrolizumab.(11)

The prevalence of MSI-H varies across tumour sites and disease stage. Several tumour sites, including endometrial, colorectal, and gastric cancers were consistently

found to have the highest MSI-H prevalence, generally above 5%.(12) For most other cancers, MSI-H prevalence was below 5%.(13) The prevalence of MSI-H at Stage IV is given in Table 3.

Table 3 Incidence of MSI-H at Stage IV from literature

	Proportion of stage IV patients with MSI-H tumours(4)
Colorectal cancer	4–8%
Endometrial cancer	6–11%
Gastric cancer	5–8%
Small intestine cancer	2–6%
Biliary cancer	1–3%

Though these cancers can occur in adults of any age, the rates of diagnosis generally increase with age and rise steeply from age 50. With the exception of endometrial cancer, the majority of the population diagnosed are male. For colorectal, endometrial and small intestine cancers there is a small to moderate increase in risk for the most deprived populations. For gastric cancer there is a sharp increase in risk with increased deprivation. The age, sex and deprivation incidence statistics for each tumour site are given in Table 4. Incidence data for MSI-H patients is limited. However, there is evidence to suggest Lynch syndrome-associated colorectal carcinoma (CRC) has an earlier age of onset, with a crude median age at diagnosis of 52 years versus 69 years in sporadic disease.(14)

Table 4 Age, sex, and deprivation incidence statistics for each tumour site, all MSI status

	Peak rate of diagnosis in the UK	**Proportion of females diagnosed in England**	**Difference in rate of incidence in most deprived quintile vs least deprived quintile in England**
Colorectal(15)	85–89	44%	5%
Endometrial cancer(16)	75–79	100%	17%
Gastric cancer(17)	85–89	35%	89%
Small intestine cancer(18)	80–84	45%	12%
Biliary cancer	Data not available	Data not available	Data not available
Source: Cancer Research UK			

CRC, endometrial and gastric cancer are within the top 20 most common cancers within the UK.(19) Biliary cancer, also referred to as cholangiocarcinoma, and small

intestine cancer are rarer. The incidence in England across these cancer types is given in Table 5.

Table 5 Incidence in England in 2020 in adult patients for the tumour sites relevant to the appraisal, all MSI status

	Incidence (all stages)(20)	Incidence for patients with stage 3 and 4 at diagnosis(20)
Colorectal cancer (ICD10 code: C18 to C20)	34,396	16,835
Endometrial cancer (ICD10 code: C54)	7,567	1,380 (ICD10 code: C54 to C55)
Gastric cancer (ICD10 code: C16)	5,053	No data available by stage
Small intestine cancer (ICD10 code: C17)	1,690	No data available by stage
Biliary cancer (ICD10 code: C22.1 and C24)	3,200	No data available by stage
Source: NHS Digital, 2020.(20)		

The indication describes patients with tumours that have advanced to an extent where curative procedures, such as tumour resection, are no longer an option. Patients at an advanced stage typically have a life expectancy of less than a year(21) and may be candidates for chemotherapies that aim to slow disease progression and lessen disease burden. The survival data specific for each tumour are presented in Table 6. Please note that the survival data presented are for patients of all MSI status as MSI-H survival data was not available.

Table 6 Age-standardized cancer survival for adult patients diagnosed at stage IV between 2015-2019, followed up to 2020, all MSI status

	1-year survival (%)(21)	3-year survival (%)(21)	5-year survival (%)(21)
CRC (ICD10 code: C18 to C20)	43.7	16.4	10.3
Endometrial cancer (ICD10 code: C54 and C55)	46.9	19.6	11.5
Gastric cancer (ICD10 code: C16)	23.2	5.3	3.8
Small intestine cancer (ICD10 code: C17)	No data available	No data available	No data available
Biliary cancer (ICD10 code: C22.1 and C24)	No data available	No data available	No data available

	1-year survival (%)(21)	3-year survival (%)(21)	5-year survival (%)(21)
Source: NHS Digital, 2022.(21)			

There is some evidence that MSI-H/dMMR status is associated with a poorer prognosis in advanced cancers. MSI-H/dMMR CRC, endometrial and gastric cancers, have been associated with poorer survival outcome in some studies in later stages compared with MSS or pMMR tumours:

- In a pooled analysis of 4 phase III studies in first-line treatment of metastatic CRC (CAIRO, CAIRO2, COIN, FOCUS): in 153 MSI-H patients median progression-free survival (PFS) and overall survival (OS) were significantly worse as compared to pMMR patients (PFS 6.2 vs 7.6 months, hazard ratio [HR] 1.33; 95% confidence interval [CI] 1.12–1.57, p = 0.001 and OS 13.6 vs 16.8 months, HR 1.35; 95% CI 1.13–1.61, p = 0.001)(22)

- From data analysed from women who participated in the Australian National Endometrial Cancer Study (ANECS) conducted between 2005 and 2007, no significant association was observed between MMR status and overall or endometrial cancer-specific survival. However, in analysis restricted to women with endometrioid histological subtype, there was evidence of a survival disadvantage for women with somatic dMMR endometrial cancer versus pMMR endometrial cancer(23)

- In a study of 285 advanced gastric cancer patients who received standard first-line chemotherapy, the median PFS times were 4.2 and 7.6 months and the objective response rates (ORR) were 31% and 49% in dMMR, and pMMR patients, respectively. Multivariate analysis showed shorter PFS in dMMR versus pMMR patients (HR, 1.97; 95% CI, 1.09-3.53; P = 0.022)(24)

There is limited evidence in the literature to draw the same conclusions in small intestine and biliary cancers.

B.1.3.2 Testing guidance

NICE recommends offering testing to all patients diagnosed with CRC or endometrial cancer to identify MSI-H/dMMR tumours.(8, 25) Often an IHC test is conducted to

identify dMMR, however for CRC a PCR test to identify MSI-H tumours is also recommended as an alternative. These tests are part of a wider testing strategy to identify patients with Lynch syndrome. Once a dMMR tumour is identified it is recommended that germline genetic testing is offered to confirm Lynch syndrome. MSI-H testing for gastric, small bowel and biliary is also featured in the National genomic test directory for cancer, and is funded by NHS England.(26)

B.1.3.3 Treatment pathway

The level of treatment guidance provided by professional bodies for each of these cancer types is varied. Guidance in colorectal cancer, endometrial cancer and gastric cancer are well established but sparse in small intestine and biliary cancers. In general, for the patients relevant to this indication, the guidance recommends established chemotherapies, with later treatment innovations such as immunotherapies introduced for some tumour sites.

Prior to 2021 there were no NICE recommended therapies for MSI-H cancer patients. More recently a few novel treatment options have been recommended for routine commissioning by NICE: pembrolizumab in MSI-H/dMMR metastatic colorectal cancer (mCRC) as first line treatment(27), and nivolumab in combination with ipilimumab for adult patients after prior fluoropyrimidine-based combination chemotherapy.(28) Nivolumab has also been accessible for patients with other MSI-H tumours through the COVID-19 interim guidance, NG161.(29) However, there is no ongoing technology appraisal for nivolumab for the above scope, and therefore there is an urgent need for patients to continue to be able to access an immunotherapy for MSI-H tumours.

NICE guidance is summarized for the tumours within the indication in Table 7.

Table 7 Summary of NICE guidance for previously treated MSI-H/dMMR patients for the relevant tumour sites within the indication

Colorectal tumours	Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA716)(28) Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405) TA716(30)

Endometrial tumours	Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779)(31)
Gastric tumours	Second-line palliative chemotherapy for people with oesophago-gastric cancer (NG83)(32)
Small intestine tumours	No guidance found
Biliary tumours	No guidance found

A summary of the European Society for Medical Oncology (ESMO) guidance is provided in Table 8. Please note where ESMO guidance is either outdated or not available the US National Comprehensive Caner Network (NCCN) guidance has been used. Some therapies in the following guidance may not be recommended by NICE.

Table 8 ESMO and NCCN Guidance for the treatment of the tumours within the indication

NCCN guidance for MSI-H/dMMR mCRC tumours(33)	Guidelines from ESMO were last published in 2014. NCCN has provided an update in 2021. Below the recommendations for the submitted indication are summarized: The panel recommends pembrolizumab or nivolumab, alone or in combination with ipilimumab, as first-line treatment options for patients with MSI-H/dMMR mCRC, whether they are eligible for intensive therapy. The panel recommends pembrolizumab, nivolumab, or nivolumab plus ipilimumab as subsequent-line treatment options in patients with metastatic MMR-deficient CRC. These therapies are only options for patients who have not previously received a checkpoint inhibitor. These patients may have received a first-line chemotherapy before their MSI-H/dMMR status was known. Listed options for first-line chemotherapy are as follows: FOLFOX, CAPEOX, FOLFIRI, infusional 5-FU/LV (fluorouracil and leucovorin) or capecitabine, and FOLFOXIRI.
ESMO guidance for MSI-H/dMMR advanced endometrial cancers(34)	The first-line standard chemotherapy (ChT) treatment is carboplatin AUC 5-6 plus paclitaxel 175 mg/m2 every 21 days for six cycles There is no standard of care for second-line ChT. Doxorubicin and weekly paclitaxel are considered the most active therapies. Immune checkpoint blockade monotherapy could be considered after platinum based therapy failure in patients with MSI-H/dMMR. Dostarlimab has recently been approved by both the EMA and the FDA for this indication Pembrolizumab–lenvatinib is approved by the EMA for EC patients who have failed a previous platinum-based ChT, and who are not candidates for curative surgery or RT. FDA approval is for EC patients whose tumours are not dMMR/MSI-H.
ESMO guidance for advanced/metastatic unresectable gastric cancer(35)	Standard first-line ChT for gastric cancer is a platinum–fluoropyrimidine doublet. Oxaliplatin and cisplatin are the most commonly used platinum drugs, whereas fluoropyrimidines may be administered as an infusion (5-FU) or as oral treatment [capecitabine or tegafur–gimeracil–oteracil]. Ramucirumab-paclitaxel is recommended for second line treatment of gastric cancer. Ramucirumab monotherapy is also an option. Where ramucirumab is not available, paclitaxel, docetaxel or irinotecan monotherapy are recommended. Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer, but trastuzumab deruxtecan may be

	considered. Pembrolizumab is recommended for second-line treatment of patients with MSI-H/dMMR gastric cancer. Alternative treatments include a taxane or irinotecan.
NCCN guidance for advanced/metastatic MSI-H/dMMR small intestine tumours(36)	No ESMO guidance has been provided for these tumours. Please see NCCN guidance below. As initial therapy for advanced disease in a patient appropriate for intensive therapy (i.e. one with a good tolerance for this therapy for whom a high tumour response rate would be potentially beneficial) without prior platinum resistance, the panel recommends a choice of 3 chemotherapy regimens: FOLFOX, CAPEOX, or FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan); any of which may be combined with bevacizumab. For patients who are not appropriate for intensive therapy, treatment options would exclude the more toxic components of these regimens, with 5-FU/LV or capecitabine with or without bevacizumab recommended as first-line therapy for these patients. For tumours that are dMMR or MSI-H, checkpoint inhibitor therapy with anti-PD-1 inhibitors, alone or in combination with an anti-CTLA4 inhibitor, is recommended in the second-line setting. FOLFIRI or taxane-based chemotherapies are options in the second line for pMMR/MSS tumours, or those that are refractory to checkpoint inhibitor therapies.
ESMO guidance for advanced/metastatic biliary tumours(37)	Cisplatin-gemcitabine is the current standard of care for first-line treatment. Oxaliplatin may be substituted for cisplatin when there is concern about renal function and gemcitabine monotherapy may be preferred in patients with a PS of 2 or other factors of fragility. There is no established second-line systemic therapy following progression after first-line treatment although fluoropyrimidine-based therapy (either in monotherapy or in combination with other cytotoxics) is sometimes used.

B.1.3.4 Positioning of pembrolizumab relative to the current treatment pathway

Pembrolizumab is anticipated to be used in clinical practice in England as a therapy for patients with a confirmed MSI-H/dMMR advanced tumour of any of the five cancer types within the indication, where:

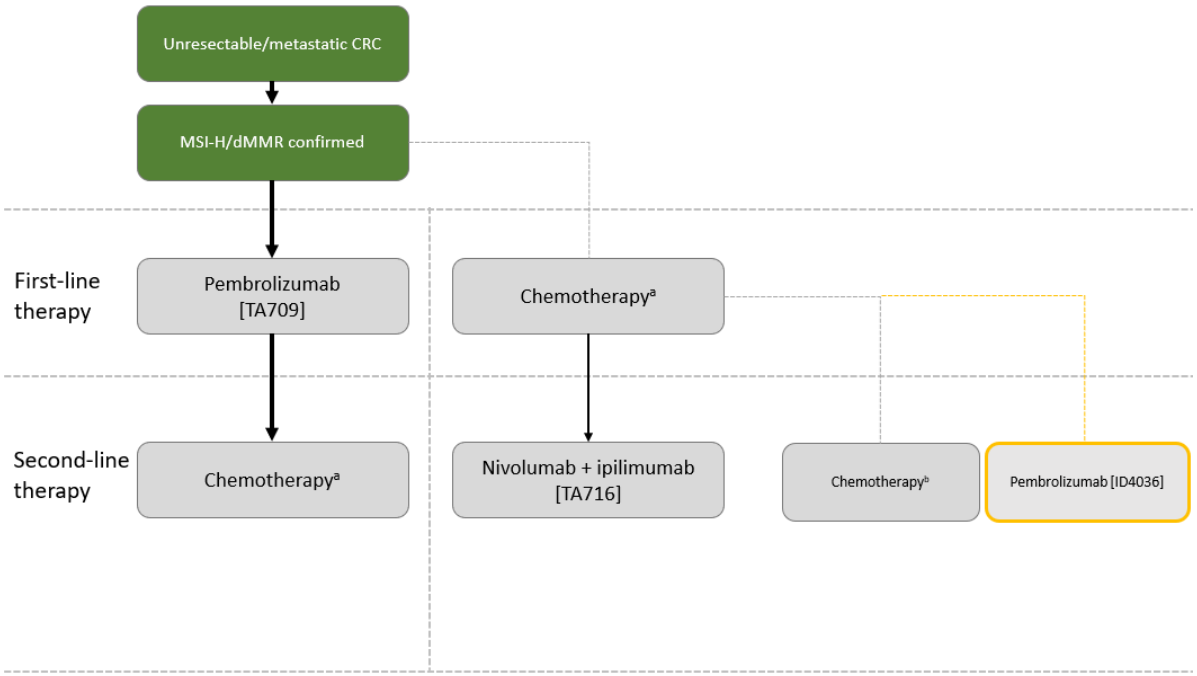
- the tumour is unresectable / where surgery is not an option,
- and at least one prior therapy has failed.

Across each of the tumour sites we anticipate pembrolizumab will be used as an alternative to a subsequent chemotherapy regimen, sparing patients of an additional course of chemotherapy treatment that is likely to be less effective compared to MSS patients. For each cancer type we outline how pembrolizumab may integrate into the current standard of care.

Chemotherapy regimens are the first- and second-line standard of care for metastatic gastric, small intestine and biliary cancers, and advanced/recurrent endometrial cancers. Here pembrolizumab can be offered as an alternative to patients otherwise limited to a second-line chemotherapy. In addition to the standard of care, dostarlimab, an immunotherapy, is currently available through the Cancer Drugs Fund (CDF) for MSI-H/dMMR endometrial cancers previously treated with a platinum-based chemotherapy.(31) However, as dostarlimab is only available through the CDF, it is not considered a comparator in this appraisal.

For metastatic MSI-H/dMMR CRC, pembrolizumab [TA709](27) is the first-line treatment of choice [redacted]. Based on clinical expert consultation(1), chemotherapy as first-line treatment is limited to those patients for which the outcome of the MSI-H/dMMR testing is still unknown or where or the progression of disease requires a fast response. This small group of patients are most commonly offered nivolumab with ipilimumab in second line.(28) This second line treatment may not be suitable for all. Some patients may have a degree of autoimmune related comorbidities which makes them unsuitable for a dual immunotherapy and CTLA-4 combination. The only alternative currently is a second chemotherapy, or pembrolizumab, subject to this appraisal. The proposed positioning of pembrolizumab to the current treatment algorithm of metastatic MSI-H/dMMR colorectal cancer, subject to this appraisal, is given in Figure 1.

Figure 1 Proposed positioning of pembrolizumab [ID4036] in the current treatment algorithm of metastatic MSI-H/dMMR colorectal cancer



Abbreviations: CRC, colorectal cancer ; dMMR, mismatch repair deficient; MSI-H, multisatellite instability-high.
Notes: Proposed position of pembrolizumab (ID4036) in current treatment pathway highlighted in yellow. [a] chemotherapy options: FOLFOX, CAPEOX, FOLFIRI, infusional 5-FU/LV or capecitabine, and FOLFOXIRI. [b] Chemotherapy options: FOLFIRI/FOLFOX/FOLFOX4/mFOLFOX6 or trifluridine-tipiracil.

As detailed in the decision problem, the most appropriate comparators for pembrolizumab in each of these tumour sites are chemotherapy regimens.

It is clear there is an unmet need for patients with MSI-H tumours whose options are limited to sequential lines of chemotherapy, given the limited survival prognosis of these advanced cancers and the evidence that suggests that these patients may have even poorer outcomes on the current standard of care than MSS patients. This technology would represent a ‘step-change’ in the management of the condition, providing an alternative therapy that may be more effective for patients with microsatellite instability, improving survival outcomes.

B.1.4 Equality considerations

No equity or equality considerations are anticipated.

B.2 Clinical effectiveness

Clinical effectiveness evidence:

- Results from the two single-arm registration studies (KEYNOTE-164 and KEYNOTE-158) showed that tumour response was achieved in more than 30% of the patients in each of the five tumour sites with objective response rate (ORR) ranging from 33.9% to 55.6%. This is considered a clinically meaningful result for patients with MSI-H solid tumours. Treatment with pembrolizumab produced durable responses, with median DOR not being reached in any of the tumour sites, except for biliary cancer. Disease control was observed in more than 50% of participants in each tumour site.

- Progression free survival (PFS) analysis was based on independent central radiologic review. At 24 months, more than 30% of participants had not progressed in any of the five tumour sites. With respect to overall survival (OS), the results suggested a prolonged treatment benefit, with more than 50% of participants in each tumour site treated with pembrolizumab still alive at 24 months.

- In KEYNOTE-158 an improvement in the EQ-5D health utility score from baseline across all participants was observed at week 9 (mean change=[redacted] points; 95% CI: [redacted]; database cutoff date: 05-OCT-2020). EQ-5D VAS score over time was stable or improved from baseline through Week 111. No patient-reported outcomes (PROs) were collected in the KEYNOTE-164 trial.

- The safety results from the two trials demonstrated that pembrolizumab is well tolerated in participants with dMMR or MSI-H across the tumour sites.

- KEYNOTE-164 and KEYNOTE-158 are two single-arm, open-label trials that investigate the use of pembrolizumab in patients with previously treated unresectable and/or metastatic mismatched repair (MMR) deficient or microsatellite Instability-High (MSI-H) solid tumours. These trials provide evidence for the population and intervention relevant to this appraisal in line with the decision problem.

- In the KEYNOTE-164 trial, a total of 124 participants were allocated to the intervention arm. The results reported in this submission are related to the final analysis (FA) (database cutoff date of 19-FEB-2021) and are presented for the pooled Cohort A and B. In the KEYNOTE-158 trial, as of database cutoff date (15-OCT-2021) a total of 183 participants in Cohort K were included in the efficacy analysis for the following MSI-H

tumour sites: endometrial (83 participants), gastric (51 participants), small intestine (27 participants), and biliary (22 participants).

Network meta-analysis:

- In the absence of RCTs comparing the efficacy of pembrolizumab directly with that of standard of care (SoC), indirect treatment comparisons (ITCs) were explored to understand the relative treatment effect of pembrolizumab versus comparators of interest.

- With the exception of gastric and endometrial cancers, no published data were identified in the SLR specifically in MSI-H/dMMR-specific populations, which is likely to result in conservative estimates of relative efficacy.

- Unanchored unadjusted ITCs were conducted for all comparators by tumour site and showed favourable OS and PFS HRs (i.e. <1) towards pembrolizumab for each comparator therapy. A matching-adjusted indirect comparison (MAIC) was only possible in the comparison with physician's choice of paclitaxel or doxorubicin in endometrial cancer, where the effective sample size was deemed sufficient, and sufficient data were available. The PFS and OS outcomes both before and after matching showed a statistically significant favourable HR (i.e., <1) towards pembrolizumab.

- Log-cumulative hazards plots for each comparator showed violation of the proportional hazard assumption. Other methods to generate time-varying HRs were not explored due to the small sample size available within each tumour site. As such, the resulting HR estimates were considered inappropriate and were not investigated further within the cost-effectiveness analysis.

Clinical effectiveness conclusions

- Overall, extended benefits associated with pembrolizumab have been observed in the trials across the five tumour sites evaluated in this appraisal. These demonstrate a positive impact from treatment with pembrolizumab in patients with MSI-H or dMMR solid tumours who currently do not have targeted treatment options and can only be offered subsequent chemotherapy regimens after first-line chemotherapies have failed.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was carried out as per NICE guidance and according to a pre-specified protocol, to identify the clinical evidence relevant to pembrolizumab and any comparator treatments for the indication of interest for this appraisal as described in Table 1. Please refer to Appendix D for full details of the process and methods used.

B.2.2 List of relevant clinical effectiveness evidence

A SLR was conducted to identify all relevant published randomized controlled trials (RCTs), single-arm and non-randomized trials relating to pembrolizumab in line with the final scope outlined in Table 1.

The SLR identified two single-arm trials (KEYNOTE-164 and KEYNOTE-158) that provided evidence on the clinical effectiveness of pembrolizumab in the patient population relevant to this appraisal (Table 9).

Table 9 Clinical effectiveness evidence

Study	**KEYNOTE-158 (NCT02628067)(38-40)**	**KEYNOTE-164 (NCT02460198)(41-43)**
Study design	Non-randomized, single arm, multi-site, open-label study	Non-randomized, single arm, multi-site, open-label study
Population	Adults with multiple types of advanced (unresectable and/or metastatic) solid tumours who have progressed on standard of care therapy. Evidence in this submission is related to the following mismatched repair (MMR) deficient or microsatellite Instability-High (MSI-H) tumour sites in line with the GB Marketing Authorization: • Endometrial cancer • Gastric cancer • Small intestine cancer • Biliary cancer (Cholangiocarcinoma)	Adults with previously-treated locally-advanced unresectable metastatic mismatched repair (MMR) deficient or microsatellite instability-high (MSI-H) colorectal carcinoma
Intervention(s)	Pembrolizumab 200 mg Q3W	Pembrolizumab 200 mg, Q3W
Comparator(s)	None	None
Indicate if study supports application for	Yes	Yes

Study	KEYNOTE-158 (NCT02628067)(38-40)	KEYNOTE-164 (NCT02460198)(41-43)
marketing authorisation		
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	ORR DOR **PFS** **OS** **Adverse Events** **HRQL**	ORR DOR **PFS** **OS** **Adverse Events**
All other reported outcomes		
Abbreviations: DOR, duration of response; HRQL, health-related quality of life; MMR, DNA mismatch repair deficient; MSI-H, microsatellite instability-high; ORR, objective response rate; OS, overall survival; PFS, progression-free survival		

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

The methodology of KEYNOTE-158 and KEYNOTE-164 trials are summarized in Table 10. Further details on eligibility criteria and concomitant medications are provided in Appendix M. Study design for KN-158 and KN-164 are depicted in Figure 2 and Figure 3, respectively.

Table 10 Summary of KEYNOTE-158 and KEYNOTE-164 methodology

	KEYNOTE-158	KEYNOTE-164
Trial design	Phase II, open-label, non-randomized, multicentre study of pembrolizumab in previously treated participants who have locally advanced unresectable or metastatic rare cancers for whom prior standard first-line treatment had failed. The study is ongoing and includes Cohorts A to M that are either tumour biomarker unselected or based on tumour biomarker expression (biomarker enrichment), as depicted in Figure 2. The results reported are from Cohort K. The criteria for	Phase II, open-label, non-randomized, multicentre study of pembrolizumab in patients with previously treated, unresectable, locally advanced or metastatic MSI-H and/or dMMR CRC. Recruitment for this study has completed. Eligible participants were recruited in Cohorts A and B. Cohort A (n=61): Participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who had been previously treated with at least 2 lines of standard of

	KEYNOTE-158	KEYNOTE-164
	Cohort K are defined as any advanced solid tumour, with the exception of colorectal carcinoma (CRC), which is microsatellite instability-high (MSI-H). MSI-H and/or dMMR status was verified by local polymerase chain reaction or immunohistochemistry (IHC) testing. Patients received pembrolizumab 200 mg every 3 weeks until progressive disease (PD), unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, administrative reasons, or the patient has received 35 trial treatments (approx. 2 years) with pembrolizumab. After the end of treatment, each participant is followed for 30 days for adverse event (AE) and events of clinical interest (ECI) monitoring and 90 days for serious AE monitoring. Participants who discontinue treatment for reasons other than disease progression have posttreatment follow-up of disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants are followed by telephone contact for OS until death, withdrawal of consent, becoming lost to follow-up or the end of the trial, whichever occurs first.	care therapies, which must have included fluoropyrimidine, oxaliplatin, and irinotecan. Cohort B (n=63): Participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who had been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan ± antivascular endothelial growth factor (anti-VEGF)/ epidermal growth factor receptor (EGFR) monoclonal antibody (mAB). MSI-H and/or dMMR status was verified by local polymerase chain reaction or immunohistochemistry (IHC) testing. Patients received pembrolizumab 200 mg every 3 weeks until progressive disease (PD), unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, administrative reasons, or the patient has received 35 trial treatments (approx. 2 years) with pembrolizumab. After the end of treatment, each participant is followed for 30 days for adverse event (AE) and events of clinical interest (ECI) monitoring and 90 days for serious AE monitoring. Participants who discontinue for reasons other than PD have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants

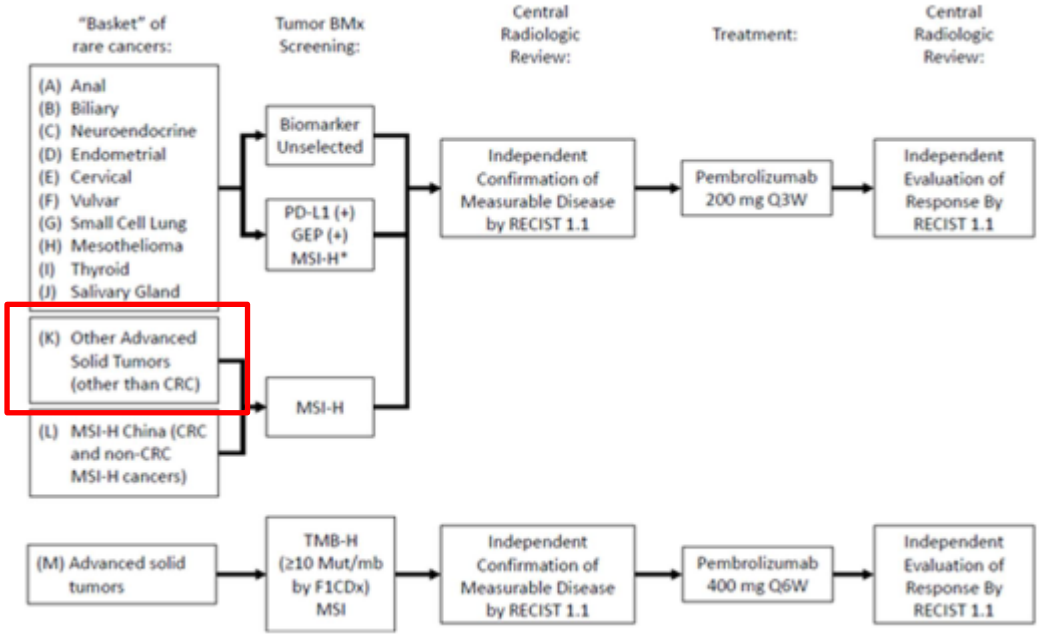
	KEYNOTE-158	KEYNOTE-164
		are followed for overall survival (OS) until death, withdrawal of consent, or the end of the study.
Eligibility criteria		
Key inclusion criteria	• ≥18 years of age on the day of signing informed consent. • A histologically or cytologically-documented, advanced (metastatic and/or unresectable) solid tumour that was incurable and for which prior standard first-line treatment had failed. • For participants in Cohort K, any advanced solid tumour (except CRC), which was MSI-H. • Radiologically measurable disease based on RECIST 1.1 confirmed by independent central radiologic review. • A performance status of 0 or 1 on the ECOG Performance Scale. • Life expectancy of at least 3 months. • Demonstrated adequate organ function.	• ≥18 years of age on the day of signing informed consent. • A histologically proven locally advanced unresectable or metastatic (Stage IV) CRC • Locally confirmed dMMR or MSI-H CRC • Previous treatment with standard of care therapies: at least 2 lines of fluoropyrimidine, oxaliplatin, and irinotecan (Cohort A) and at least 1 line of systemic fluoropyrimidine +oxaliplatin or fluoropyrimidine + irinotecan ± anti-VEGF/EGFR mAB (Cohort B) • An ECOG PS of 0 or 1 • A life expectancy of greater than 3 months • At least 1 measurable lesion by RECIST 1.1 as determined by central review for response assessment • Demonstrated adequate organ function.
Key exclusion criteria	• Had participated in any other pembrolizumab trial or received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or any other immune-modulating mAB. • A diagnosis of immune deficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. • An active autoimmune disease that had required systemic treatment in the past 2 years. • A prior anti-cancer mAB within 4 weeks prior to study Day 1 or had not recovered (i.e. ≤ Grade 1 or at baseline)	• An active autoimmune disease that had required systemic treatment in the past 2 years (i.e. with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) • A diagnosis of immunodeficiency or receipt of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment • Known active CNS metastases and/or carcinomatous meningitis • Prior mAB, chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study

	KEYNOTE-158	KEYNOTE-164
	from an AE due to mABs administered more than 4 weeks earlier. • Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or had not recovered (i.e. ≤ Grade 1 or at baseline) from an AE due to a previously administered agent. • A known additional malignancy within 2 years prior to enrolment. • Known active CNS metastases and/or carcinomatous meningitis	Day 1 or participant who had not recovered (i.e. ≤ Grade 1 or at baseline) from AEs due to a previously administered agent • Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
Settings and locations where the data were collected	This study was conducted at 54 centres in 18 countries. No patients were recruited in the UK.	This study was conducted at 34 centres in 10 countries. No patients were recruited in the UK.
Trial drugs	Trial drug: pembrolizumab Dosage formulation: solution for infusion Dose strength: 25 mg/mL (100 mg/4 mL) Dose and regimen: 200 mg, Q3W, administered of Day 1 of each 21-day cycle Route of administration: IV infusion	
Study Objectives		
Primary Objectives	To evaluate the ORR to pembrolizumab, based on RECIST 1.1 as assessed by independent central radiologic review, in biomarker selected participants with any one of multiple types of advanced (metastatic and/or unresectable) solid tumours (Cohorts A to K)	Objective (Cohort A): To evaluate the ORR per RECIST 1.1 assessed by independent radiologist review of the 200 mg Q3W dose of pembrolizumab in participants with locally advanced unresectable or metastatic MMR deficient or MSI high CRC and who have been previously treated with standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan. Objective (Cohort B): To estimate the ORR per RECIST 1.1 assessed by central imaging vendor of the 200 mg Q3W dose of pembrolizumab in participants with locally advanced unresectable or metastatic MMR deficient or MSI high CRC and who have been

	KEYNOTE-158	KEYNOTE-164
		previously treated with at least one line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody).
Secondary Objectives	• To determine the safety and tolerability of pembrolizumab • To evaluate DOR (based on RECIST 1.1 as assessed by independent central radiologic review) in participants receiving pembrolizumab • To evaluate PFS (based on RECIST 1.1 as assessed by independent central radiologic review) in participants receiving pembrolizumab • To evaluate OS in participants receiving pembrolizumab	In both Cohort A and Cohort B separately: • To determine safety and tolerability of pembrolizumab. • To evaluate duration of response (DOR), disease control rate (DCR) and progression-free survival (PFS) per RECIST 1.1 assessed by central imaging vendor and overall survival (OS).
Exploratory Objectives	• To compare ORR, DOR, and PFS based on irRECIST with these same measures derived using RECIST 1.1, both as assessed by independent central radiologic review • To describe the change in Patient-Reported Outcome scores between baseline and postbaseline time points overall and according to the subgroup of best overall response using the EuroQol EQ-5D and EORTC QLQ-C30 instruments.	For Cohorts A and B separately: • To evaluate ORR, DOR, DCR and PFS per RECIST 1.1 assessed by investigator. • To evaluate ORR, DOR, DCR and PFS per irRECIST 1.1 assessed by central imaging vendor. • To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab.

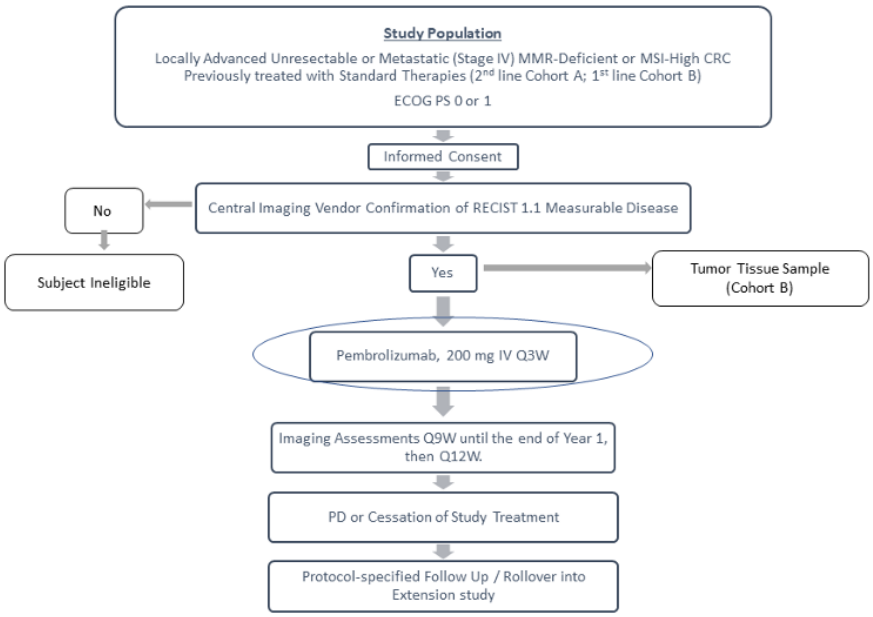
Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficient; DOR, duration of response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; IHC, immunohistochemistry; mAB, monoclonal antibody; MSI-H, microsatellite instability-high; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks

Figure 2 KEYNOTE-158 study design



Notes: Results are reported for four tumour sites within Cohort K: endometrial cancer, gastric cancer, small intestine cancer and biliary (cholangiocarcinoma) cancer.
Source: MSD Data on File. KEYNOTE-158 Protocol.(44)

Figure 3 KEYNOTE-164 study design



Source: MSD Data on File. KEYNOTE-164 Protocol.(45)

B.2.3.1 Baseline characteristics of trial participants

Baseline characteristics are summarized in Table 11 and Table 12. Overall, the demographic and baseline characteristics in the study population in both studies were generalizable to the patients in the UK.

B.2.3.1.1 KEYNOTE-164 trial (Colorectal cancer)

Around two thirds of participants were white (67.7%) and less than or equal to 65 years of age (66.9%). The majority of participants had an ECOG PS of 1 (58.9%), all were stage IV and none had a history of brain metastases. The majority of participants had no prior adjuvant or neoadjuvant therapy (69.4%).

Table 11 Participant characteristics (ASaT population)

	Total	
	n	(%)
Participants in population	124	
Sex		
Male	69	(55.6)
Female	55	(44.4)
Age (Years)		
<=65	83	(66.9)
>65	41	(33.1)
Mean	56.1	
SD	14.9	
Median	55.5	
Range	21 to 84	
Race		
Asian	33	(26.6)
Black Or African American	7	(5.6)
White	84	(67.7)
Ethnicity		
Hispanic Or Latino	4	(3.2)
Not Hispanic Or Latino	119	(96.0)
Not Reported	1	(0.8)
ECOG PS		
0	51	(41.1)
1	73	(58.9)
Cancer Stage		
IV	124	(100.0)
Metastatic Staging		
M0	4	(3.2)
M1	120	(96.8)
History of Brain Metastases		
No	124	(100.0)

	Total	
	n	(%)
MSI-High Status[a]		
POSITIVE	123	(99.2)
NEGATIVE	1	(0.8)
KRAS Status		
MUTANT	39	(31.5)
WILD TYPE	74	(59.7)
NRAS Status		
MUTATION DETECTED	7	(5.6)
MUTATION NOT DETECTED	56	(45.2)
UNDETERMINED	61	(49.2)
Mutation Status (Tougeron)[b]		
MUTANT	15	(12.1)
WILD TYPE	61	(49.2)
UNDETERMINED	48	(38.7)
BRAF Status		
MUTANT	15	(12.1)
WILD TYPE	61	(49.2)
UNDETERMINED	48	(38.7)
Prior Adjuvant/Neo-Adjuvant Therapy		
Yes	38	(30.6)
No	86	(69.4)
Baseline Tumour Size (mm) Based on IRC Assessment per RECIST 1.1		
Participants with data	124	
Mean	98.2	
SD	78.9	
Median	77.0	
Range	10.4 to 407.6	

Number of participants: all-participants-as-treated population, Cohort A and Cohort B
Cohort A: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least 2 lines of standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan
Cohort B: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody)
a: MSI status by PCR test or IHC test at local site laboratory
b: A participant with a KRAS or NRAS status of Mutant is classified as Mutant. A participant with a KRAS status of Wild Type and NRAS status of Mutation Not Detected is classified as Wild Type, else the participant is classified as Undetermined
Database Cutoff Date: 19FEB2021

B.2.3.1.2 KEYNOTE-158 trial

With the exception of endometrial, there were more males in the trial. The majority of participants were white (78.7%), and more than half (53.5%) were < 65 years of age. At the time of study entry, the majority of participants had stage IV cancer and nearly

half of the participants had received 2 or more lines of therapy for their metastatic or unresectable disease.

Table 12 Participant characteristics (ASaT population)

	Pembrolizumab 200 mg Q3W							
	Endometrial		Gastric		Small Intestine		Cholangiocarcinoma	
	n	%	n	%	n	%	n	%
Participants in population	83		51		27		22	
Sex								
Male			33	65%	17	63%	16	73%
Female	83	100%	18	35%	10	37%	6	27%
Age (Years)								
< 65	45	54%	22	43%	18	67%	13	59%
>= 65	38	46%	29	57%	9	33%	9	41%
Mean	64.3		66.2		57.6		59.7	
SD	8.7		11.9		13.1		11.1	
Median	64		67		58		60.5	
Range	42 to 86		41 to 89		21 to 77		40 to 77	
Race								
American Indian Or Alaska Native	1	1%	3	6%	2	7%		
Asian	5	6%	14	28%	3	11%	2	9%
Black Or African American	3	4%	2	4%				
Multiple	2	2%	2	4%				
White, Asian	2	2%						
White	70	84%	32	63%	22	82%	20	91%
Missing	2	2%						
Ethnicity								
Hispanic Or Latino	13	16%	6	12%	3	11%	2	9%
Not Hispanic Or Latino	60	72%	40	78%	20	74%	18	82%
Not Reported	10	12%	4	8%	4	15%	2	9%
Unknown			1	2%				
Geographic Region								
US	16	19%	4	8%	7	26%	2	9%
Non-US	67	81%	47	92%	20	74%	20	91%
ECOG								
[0] Normal Activity	38	46%	23	45%	15	56%	10	46%
[1] Symptoms, but ambulatory	45	54%	28	55%	12	44%	12	55%
Metastatic Staging								
M0	2	2%	0		1	4%	4	18%
M1	81	98%	51	100%	26	96%	18	82%
Overall Stage								
III							1	5%
IIIA					1	4%		
IIIB							1	5%
IIIC	2	2%						
IV	67	81%	47	92%	26	96%	14	64%
IVA							1	5%
IVB	14	17%	4	8%			5	23%
Brain Metastases Present								
Yes			1	2%				
No	83	100%	50	98%	27	100%	22	100%

	Pembrolizumab 200 mg Q3W							
	Endometrial		Gastric		Small Intestine		Cholangiocarcinoma	
	n	%	n	%	n	%	n	%
Number of Prior Lines of Therapy								
0					2	7%	2	9%
1	44	53%	28	55%	15	56%	11	50%
2	20	24%	11	22%	6	22%	6	27%
3	13	16%	9	18%	3	11%	1	5%
4	5	6%	2	4%	1	4%	2	9%
5 or more	1	1%	1	2%				
Sum of Target Lesions Measurable at Baseline (mm)								
Participants with data	83		51		27		22	
Mean	91.9		78.9		63		89.9	
SD	70.8		60.4		38.9		61.3	
Median	71.1		62.9		55.3		80.8	
Range	11.8 to 282.8		14.4 to 255.9		14.8 to 165.5		21.3 to 231.1	
Prior Radiation Therapy								
Yes	54	65%	14	28%	2	7%	3	14%
No	29	35%	37	73%	25	93%	19	86%
PD-L1 Status								
Positive	10	12%	6	12%	2	7%	3	14%
Negative	2	2%	5	10%	5	19%	2	9%
Not Evaluable	1	1%						
Missing	70	84%	40	78%	20	74%	17	77%
Notes: PD-L1 positive was based on CPS >=1. Database Cutoff Date: 15OCT2021.								

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

B.2.4.1 Statistical analysis and definition of study groups in the KEYNOTE-158 and KEYNOTE-164 study

Study objective and endpoints and statistical methods are described in Table 13.

Table 13 Statistical analysis and definition of study groups in KEYNOTE-158 and KEYNOTE-164

	KEYNOTE-158	KEYNOTE-164
Treatment Assignment	As it is a single treatment arm, participants were assigned to pembrolizumab by non-random assignment. The trial was open-label: the Sponsor, investigator and participant were aware of the treatment administered.	As it is a single treatment arm, participants were assigned to pembrolizumab by non-random assignment The trial was open-label: the Sponsor, investigator and participant were aware of the treatment administered.
Efficacy Analysis Populations	All Subjects as Treated (ASaT) population for efficacy analysis defined as participants who	All Subjects as Treated (ASaT) population which included all

	KEYNOTE-158	KEYNOTE-164
	received at least 1 dose of study intervention and the opportunity to have been followed for 6 months prior to data cut off. As of 15-OCT-2021, a total of 183 participants in Cohort K were included in the ASaT population for efficacy analysis for the following MSI-H tumour sites: endometrial (83 participants), gastric (51 participants), small intestine (27 participants), and biliary (22 participants).	allocated participants who received at least 1 dose of pembrolizumab. A total of 124 participants were included in the ASaT population (61 in Cohort A and 63 in Cohort B).
Safety Analysis Populations	ASaT population defined as allocated subjects who have received at least one dose of study treatment.	ASaT population
Primary Endpoint	ORR based on RECIST 1.1 as assessed by independent central radiologic review (IRC) – ORR is defined as the proportion of participants in the analysis population (ASaT) who have a confirmed complete response (CR) or partial response (PR).	ORR based on RECIST 1.1 as assessed by independent radiologist review (IRC). ORR is defined as the proportion of the participants in the analysis population who have a complete response (CR) or partial response (PR).
Secondary Endpoint	DOR, based on RECIST 1.1 as assessed by IRC. DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause (whichever occurs first). PFS, based on RECIST 1.1 as assessed by IRC. PFS is defined as the time from allocation to the first documented disease progression or death due to any cause (whichever occurs first). OS is defined as the time from allocation to death due to any cause. Safety endpoints - Safety assessments included adverse events (AEs), serious AEs and Adverse event of special Interest (AEOSI)	Safety and tolerability - The primary safety analysis was based on participants who experienced toxicities as defined by CTCAE, Version 4.0 criteria DCR, based on RECIST 1.1 assessed by central imaging vendor. DCR is defined as the percentage of participants who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks prior to any evidence of progression. DOR, based on RECIST 1.1 assessed by central imaging vendor. For participants who demonstrate CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death

	KEYNOTE-158	KEYNOTE-164
		due to any cause, whichever occurs first. PFS, based on RECIST 1.1 assessed by central imaging vendor. PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. OS is defined as the time from first day of study treatment to death due to any cause. Participants without documented death at the time of analysis were censored at the date of the last follow-up.
Statistical Methods for Key Efficacy Analyses	The point estimate and 95% confidence interval (CI) for the ORR, based on IRC using RECIST 1.1, were provided using an exact binomial distribution (Clopper and Pearson method). Participants without response data were counted as non-responders. DOR and PFS, based on IRC review using RECIST 1.1, were summarized by Kaplan–Meier (KM) methods. OS was summarized by KM methods. Participants were censored at last assessment if there was no PFS or OS event.	In Cohort A, the point estimate, 95% confidence interval, and p-value for testing the response rate is greater than 15% were provided using exact binomial method proposed by Clopper and Pearson. In Cohort B, the point estimate and 95% confidence interval were provided using exact binomial method proposed by Clopper and Pearson. Participants in the primary analysis population (ASaT) without ORR data were counted as non-responder. For DCR, the point estimate, 95% confidence interval were provided using exact binomial method proposed by Clopper and Pearson. Participants in the analysis population (ASaT) with missing DCR are considered as disease not under control. For DOR, Kaplan–Meier (KM) curves and median estimates from the KM curves were provided as appropriate. For PFS and OS endpoints, KM curves and median estimates from the KM

	KEYNOTE-158	KEYNOTE-164
		curves were provided as appropriate.
Statistical Methods for Key Safety Analyses	Safety was evaluated using descriptive statistics.	Safety and tolerability were assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs for each cohort separately. Count and percentage of AE were provided.
Interim and Final Analyses	The trial incorporates an adaptive design in which multiple interim analyses may be performed with the opportunity to modify the planned sample size.	Interim Analysis For Cohort A, an interim analysis was planned. Timing: Was performed when the first 40 participants were followed up for at least 18 weeks There is no interim analysis planned for Cohort B. Final Analysis Timing: Performed when all patients have been followed up for at least 6 months.
Multiplicity	There is no planned multiplicity control for this trial. The study is an adaptive trial. The cumulative data are reviewed by the study team on an ongoing basis, with no multiplicity control.	Cohort A and Cohort B have been evaluated independently. No multiplicity adjustment in each cohort.
Sample Size and Power	The study is still recruiting and may enrol up to approximately 350 participants with any of the tumour types eligible in Cohort K (MSI-H). As of 15-OCT-2021, a total of 183 participants in Cohort K were allocated in the ASaT population for efficacy analysis for the following MSI-H tumour sites: endometrial (83 participants), gastric (51 participants), small intestine (27 participants), and biliary (22 participants).	The overall sample size is approximately 120. Cohort A: The planned sample size was 60 participants. For the ORR per RECIST 1.1 assessed by independent radiologist review, the trial has 93% power to demonstrate that ORR of pembrolizumab is better than 15% at an overall one-sided 2.5% alpha level, if the underlying centrally reviewed RECIST 1.1 ORR of pembrolizumab is 35%. Cohort B: The planned sample size was 60 participants.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of the KEYNOTE-164 and KEYNOTE-158 trials was performed using Newcastle-Ottawa quality assessment scale for cohort studies. The results of

the quality assessment show low risk of bias across all relevant domains. Full details of the SLR, including methods and results can be found in Appendix D.

B.2.6 Clinical effectiveness results of the relevant studies

Clinical effectiveness results from KEYNOTE-164 (colorectal cancer) and KEYNOTE-158 (endometrial, gastric, small intestine and biliary cancers) are provided in sections B.2.6.1 and B.2.6.2, respectively. Please note in some figures pembrolizumab is referred to as MK-3475.

B.2.6.1 KEYNOTE-164 trial (colorectal cancer)

The data reported in this submission for the KEYNOTE-164 study are the results of the final analysis (FA) with a database cutoff date of 19-FEB-2021. Results are reported for the pooled Cohort A and B.

B.2.6.1.1 Participant disposition and follow-up duration

A total of 124 participants were allocated (61 in Cohort A and 63 in Cohort B). A total of [redacted] participants completed the study treatment and [redacted] discontinued the study treatment (Appendix D.3.1).

The median follow-up duration (defined as the time from first day of study treatment to the date of death or the database cutoff date if the patient was still alive) was [redacted] months (range: [redacted]) for Cohort A and [redacted] months (range: [redacted] for Cohort B (Table 14).

Table 14 Summary of follow-up duration by cohort (ASaT population)

Study: KEYNOTE-164	**Pembrolizumab 200mg Q3W**
Follow-up duration (months)† Median (Range) Cohort A (N= 61) Median (Range) Cohort B (N= 63)	 31.4 [redacted] 52.7 [redacted]
† Follow-up duration is defined as the time from first day of study treatment to the date of death or the database cutoff date if the patient was still alive. (Database Cutoff Date: 19FEB2021).	

B.2.6.1.2 Primary efficacy analysis

B.2.6.1.2.1 Objective response rate (ORR)

In the ASaT population, pembrolizumab monotherapy provided clinically meaningful anticancer activity with respect to ORR. Forty-two participants achieved an independent radiologist review committee (IRC)-confirmed objective response, resulting in an ORR of 33.9% (95% CI: 25.6, 42.9); complete response (CR) was achieved in 9.7% (95% CI: 5.1, 16.3) of participants (Table 15). Disease control was achieved in 53.2% (95%: 44.1, 62.2) of participants.

Table 15 Summary of best objective response based on RECIST 1.1 per central radiology assessment – Pooled Cohorts a and B (ASaT population)

Study: KEYNOTE-164	Total N = 124	
Response evaluation	**n**	**Percentage [95 %-CI]**
Objective response (CR+PR)	42	33.9 [25.6; 42.9]
Complete response (CR)	12	9.7 [5.1; 16.3]
Partial response (PR)	30	24.2 [17.0; 32.7]
Stable disease (SD)	24	19.4 [12.8; 27.4]
Disease control (CR+PR+SD)	66	53.2 [44.1; 62.2]
Progressive disease (PD)	53	42.7 [33.9; 51.9]
Non-evaluable (NE)	5	4.0 [1.3; 9.2]

Only confirmed responses are included
Based on binomial exact confidence interval method
Number of participants: all-subjects-as-treated population, Cohort A and Cohort B
Cohort A: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least 2 lines of standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan
Cohort B: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody)
Database Cutoff Date: 19FEB2021

B.2.6.1.3 Secondary analysis

B.2.6.1.3.1 Duration of response (DOR)

Among participants who achieved a response (n=42), treatment with pembrolizumab produced durable responses, with >90% of responders having an ongoing response for ≥156 weeks, by Kaplan–Meier (KM) estimation (Figure 4). As of FEB-2021 data cutoff, median DOR was not reached (range: 19.3-254.4+ weeks, where "+" indicates an ongoing response as of the data cutoff date). Time to response and duration of response are provided in Table 16.

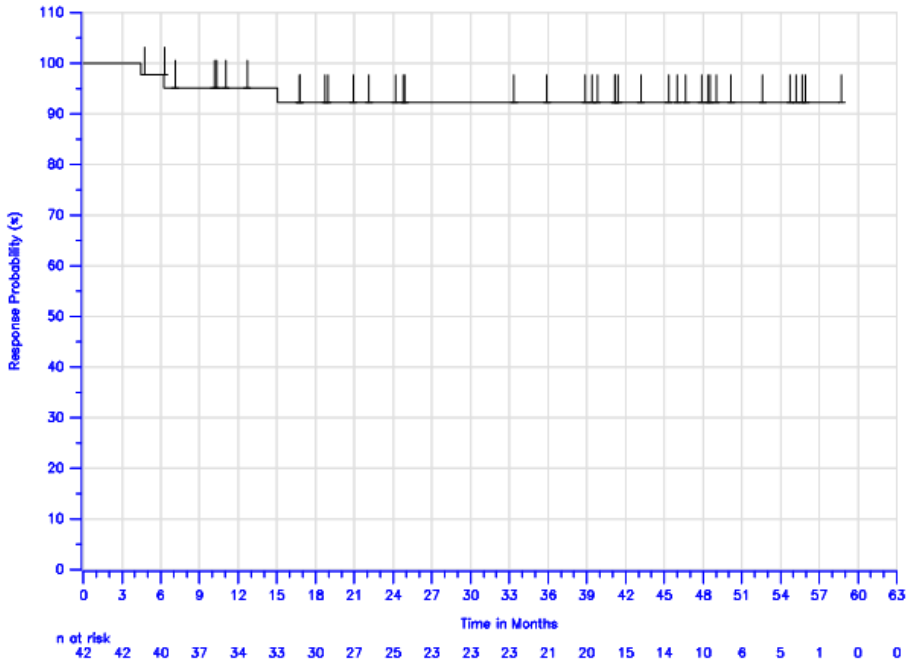
Table 16 Summary of time to response and response duration in participants with confirmed response based on RECIST 1.1 per central radiology assessment – Pooled Cohorts A and B (ASaT population)

Study: KEYNOTE-164	Total (N=124)
Number of participants with response[†]	42
Time to Response (weeks)	
Mean (SD) Median (Range)	27.0 (27.6) 17.9 (7.9-136.1)
Response Duration[‡] (weeks)	
Median (Range)	NR (19.3 - 254.4+)

Study: KEYNOTE-164	Total (N=124)
Number (%‡) of Participants with Extended Response Duration:	
≥26 weeks	40 (97.6)
≥52 weeks	34 (95.1)
≥78 weeks	30 (92.2)
≥104 weeks	26 (92.2)
≥156 weeks	21 (92.2)

Number of participants: all-subjects-as-treated population, Cohort A and Cohort B
† Includes participants 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; SD = Standard Deviation
Database Cutoff Date: 19FEB2021

Figure 4 KM estimates of objective response (confirmed) duration based on RECIST 1.1 per central radiology assessment – Pooled Cohorts A and B (ASaT population)



Notes: Data cutoff date: 19FEB2021.

B.2.6.1.3.2 Progression-free survival (PFS)

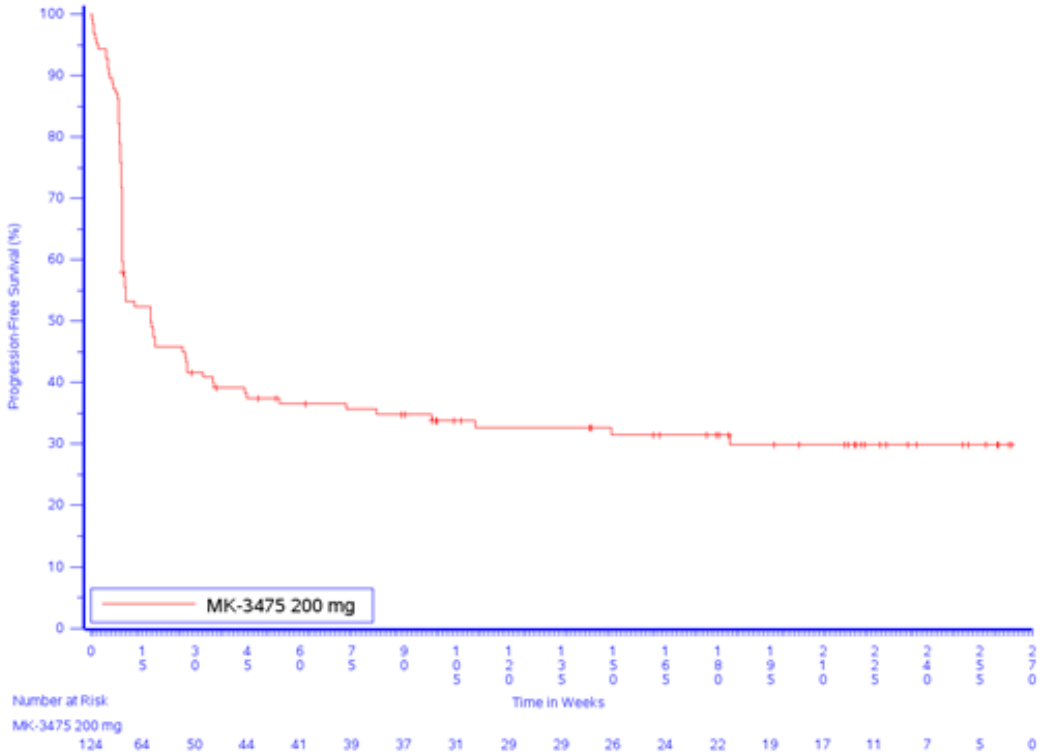
Table 17 shows PFS results in the ASaT population based on independent central radiologist review. As of the February 2021 data cutoff, PFS events were observed in 84 (67.7%) participants. Median PFS was 4.0 months (95% CI: 2.1, 7.4) (Figure 5). At 36 months, more than 30% of participants had not progressed.

Table 17 Estimated median and mean of PFS based on RECIST 1.1 per central radiology assessment – Pooled Cohorts A and B (ASaT population)

Study: KEYNOTE-164 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 200 mg Q3W	124	84 (67.7)	17.3	[redacted]	[redacted]	[redacted]	[redacted]

Number of participants: all-participants-as-treated population, Cohort A and Cohort B
Cohort A: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least 2 lines of standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan
Cohort B: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody)
Estimated median and mean time is from product-limit (Kaplan–Meier) method
Progression-free survival is defined as the time from first day of study treatment to the first documented disease progression (based on IRC assessment) or death due to any cause, whichever occurs first
Database Cutoff Date: 19FEB2021

Figure 5 KM estimates of PFS based on RECIST 1.1 per central radiology assessment – Pooled Cohorts A and B (ASaT population)



Notes: Database cutoff date: 19FEB2021.

Table 18 Summary of PFS based on IRC assessment per RECIST 1.1 – Pooled Cohorts A and B (ASaT population)

Study: KEYNOTE-164	Pembrolizumab 200mg Q3W
Participants in population	124
Number (%) of PFS Events	84 (67.7)

Study: KEYNOTE-164	Pembrolizumab 200mg Q3W
Person-Months	1924
Event Rate/100 Person-Months (%)	4.4
Median PFS (Months)§	4.0
95% CI for Median PFS§	[redacted]
PFS rate at 6 Months in % §	45.8
PFS rate at 12 Months in % §	37.5
PFS rate at 24 Months in % §	33.8
PFS rate at 36 Months in % §	31.5
Progression-free survival is defined as time from first day of study treatment to disease progression, or death, whichever occurs first. § From product-limit (Kaplan–Meier) method for censored data. (Database Cutoff Date: 19FEB2021).	

B.2.6.1.3.3 Overall survival (OS)

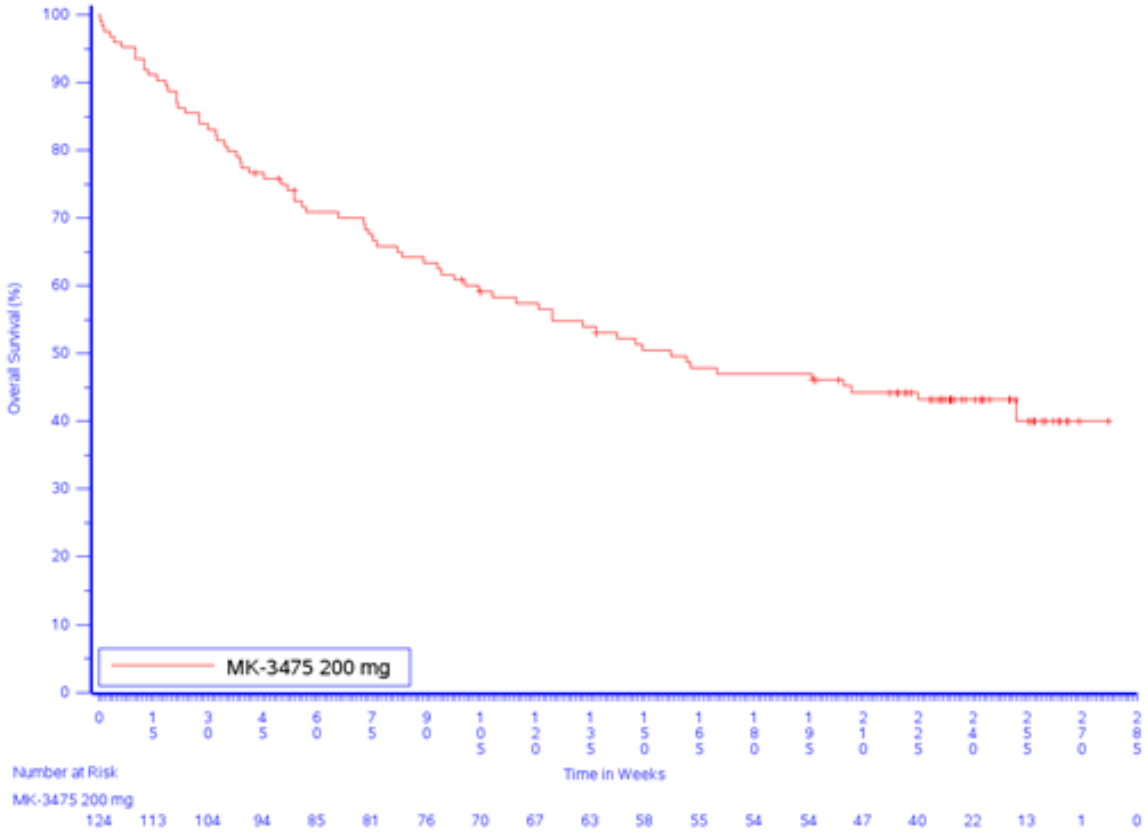
In the ASaT population, treatment with pembrolizumab suggested a prolonged benefit with respect to OS. As of FEB-2021 data cutoff, death events occurred in 69 (55.6%) participants (Table 19). The median OS was 36.1 months (95%CI: 24.0, NR) (Figure 6) with more than 50% of participants being still alive at 36 months (Table 20).

Table 19 Estimated median and mean of overall survival – Pooled Cohorts A and B (ASaT population)

Study: KEYNOTE-164 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 200mg Q3W	124	69 (55.6)	157.1	(104.3, -)	151.5	9.0	(133.8, 169.1)

Number of participants: all-subjects-as-treated population, Cohort A and Cohort B
Estimated median and mean time is from product-limit (Kaplan–Meier) method
Overall survival is defined as the time from first day of study treatment to death due to any cause
Database Cutoff Date: 19FEB2021

Figure 6 KM estimates of overall survival – Pooled Cohorts A and B (ASaT population)



Notes: Database cutoff date: 19FEB2021.

Table 20 Summary of overall survival – Pooled Cohorts A and B (ASaT population)

	Pembrolizumab 200mg Q3W
Participants in population	124
Number (%) of Events	69 (55.6)
Person-Months	3985
Event Rate/100 Person-Months (%)	1.7
Median OS (Months)§	36.1
95% CI for Median OS§	(24.0,.)
OS rate at 12 Months in % §	74.2
OS rate at 24 Months in % §	59.1
OS rate at 36 Months in % §	50.5
OS rate at 48 Months in % §	44.3

OS: Overall survival
§ From product-limit (Kaplan–Meier) method for censored data.
(Database Cutoff Date: 19FEB2021).

B.2.6.1.3.4 Patient-reported outcomes

No PROs were collected in this study.

B.2.6.2 KEYNOTE-158 trial (database cutoff date: 15-OCT-2021)

The data reported in this submission represent the results of the interim analysis 13 (IA13), with a database cutoff date of 15-OCT-2021.

B.2.6.2.1 Patient disposition and follow-up duration

A total of 183 participants across the four tumour sites relevant to this appraisal were allocated to Cohort K. All allocated participants received at least one dose of study intervention. A majority of participants had discontinued pembrolizumab, mostly due to progressive disease. Nearly half of the participants had discontinued the study; the most common reason was death (Appendix D.3.2).

The median duration of follow-up (defined as the time from first day of study treatment to the date of death or the database cutoff date if the patient was still alive) of participants in the ASaT population for efficacy analysis (ASaT population with 6 months follow-up, n=183) by tumour site is shown in Table 21.

Table 21 Summary of follow-up duration by tumour site (ASaT population for efficacy analysis)

Tumour site	N	Follow-up duration (months)[a]	
		Median (Range)	Mean (SD)
Endometrial	83	21.9 (1.5, 64.0)	28.3 (21.1)
Gastric	51	13.9 (1.1, 66.9)	22.2 (22.4)
Small intestine	27	29.1 (4.2, 67.7)	34.9 (22.1)
Cholangiocarcinoma	22	19.4 (1.1, 60.8)	25.3 (20.2)

[a] Follow-up duration is defined as the time from first dose to the date of death or the database cutoff date if the participant is still alive.
Participants who received at least one dose of pembrolizumab in KN158 with MSI-H tumours in cohort K with 6 months follow-up are included.
(Database Cutoff Date: 15OCT2021).

B.2.6.2.2 Primary efficacy analysis

B.2.6.2.2.1 Objective response rate

ORR data by tumour site for the participants that have been followed for 6 months prior to data cutoff (ASaT population for efficacy analysis) are provided in Table 22. Pembrolizumab monotherapy provided clinically meaningful anticancer activity with respect to ORR across the four tumour sites ([redacted]%, 95%CI: [redacted]) (Figure 7).

Table 22 Summary of best objective response based on RECIST 1.1 per central radiology assessment by tumour site (ASaT population for efficacy analysis)

Tumour site	N	Objective response (CR+PR)	Complete response (CR)	Partial response (PR)	Stable disease (SD)	Disease control (CR+PR+SD)	Progressive disease (PD)	Non-evaluable (NE)	No assessment
		n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]
Endometrial	83	42 (50.6) (39.4, 61.8)	13 (15.7) (8.6, 25.3)	29 (34.9) (24.8, 46.2)	16 (19.3) (11.4, 29.4)	58 (69.9) (58.8, 79.5)	22 (26.5) (17.4, 37.3)	1 (1.2) (0.0, 6.5)	2 (2.4) (0.3, 8.4)
Gastric	51	19 (37.3) (24.1, 51.9)	7 (13.7) (5.7, 26.3)	12 (23.5) (12.8, 37.5)	7 (13.7) (5.7, 26.3)	26 (51.0) (36.6, 65.2)	18 (35.3) (22.4, 49.9)	1 (2.0) (0.0, 10.4)	6 (11.8) (4.4, 23.9)
Small intestine	27	15 (55.6) (35.3, 74.5)	4 (14.8) (4.2, 33.7)	11 (40.7) (22.4, 61.2)	6 (22.2) (8.6, 42.3)	21 (77.8) (57.7, 91.4)	5 (18.5) (6.3, 38.1)	0 (0.0) (0.0, 12.8)	1 (3.7) (0.1, 19.0)
Cholangiocarcinoma	22	9 (40.9) (20.7, 63.6)	3 (13.6) (2.9, 34.9)	6 (27.3) (10.7, 50.2)	3 (13.6) (2.9, 34.9)	12 (54.5) (32.2, 75.6)	8 (36.4) (17.2, 59.3)	0 (0.0) (0.0, 15.4)	2 (9.1) (1.1, 29.2)

[a] Based on binomial exact confidence interval method. Only confirmed responses are included.
'No Assessment' (NA) counts participants who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.
(Database Cutoff Date: 15OCT2021).

Figure 7 Forest plot of objective response rate by tumour site based on RECIST 1.1 per central radiology assessment (ASaT population for efficacy analysis)

Notes: Only confirmed responses are included. Database cutoff date: 15OCT2021.

Endometrial

Among the 83 participants with MSI-H endometrial tumours, 42 participants achieved an IRC-confirmed objective response, resulting in an ORR of 50.6% (95% CI: 39.4, 61.8); complete response (CR) was achieved in 15.7% (95% CI: 8.6, 25.3) of participants. Disease control was achieved in 69.9% (95%CI: 58.8, 79.5) of participants.

Gastric

Among the 51 participants with MSI-H gastric tumours, 19 participants achieved an IRC-confirmed objective response, resulting in an ORR of 37.3% (95% CI: 24.1, 51.9); CR was achieved in 13.7% (95% CI: 5.7, 26.3) of participants. Disease control was achieved in 51.0% (95%CI: 36.6, 65.2) of participants.

Small intestine

Among the 27 participants with MSI-H small intestine tumours, 15 participants achieved an IRC-confirmed objective response, resulting in an ORR of 55.6% (95% CI: 35.3, 74.5); CR was achieved in 14.8% (95% CI: 4.2, 33.7) of participants. Disease control was achieved in 77.8% (95%CI: 57.7, 91.4) of participants.

Biliary

Among the 22 participants with MSI-H biliary tumours, 9 participants achieved an IRC-confirmed objective response, resulting in an ORR of 40.9% (95% CI: 20.7, 63.6); CR was achieved in 13.6% (95% CI: 2.9, 34.9) of participants. Disease control was achieved in 54.5% (95%CI: 32.2, 75.6) of participants.

B.2.6.2.3 Secondary analysis

B.2.6.2.3.1 Duration of response (DOR)

Among responders, treatment with pembrolizumab produced durable responses across the four tumour sites, with more than 40% of responders in each tumour site having an extended response duration of ≥36 months, by KM estimation. Median DOR was not reached for any of the tumour sites, except for biliary (Figure 8). Time to response and duration of response by tumour site are provided in Table 23.

Table 23 Summary of time to response and duration of response based on RECIST 1.1 per central radiology assessment by tumour site in participants with confirmed response (ASaT population for efficacy analysis)

Study: KEYNOTE-158	Endometrial (N=83)	Gastric (N=51)	Cholangio-carcinoma (N=22)	Small intestine (N=27)
Number of participants with response[a]	42	19	9	15
Time to Response (months)				
Mean (SD) Median (Range)	3.5 (2.6) 2.1 (1.3-12.7)	3.5 (1.5) 3.8 (1.9-6.5)	3.0 (1.1) 2.4 (1.9-4.2)	4.2 (4.7) 2.1 (1.9-17.9)
Response Duration[b] (months)				
Median (Range)	NR (2.9 - 60.4+)	NR (6.2 - 63.0+)	30.6 (6.2 - 46.0+)	NR (3.7+ - 57.3+)
Number (%[b]) of Participants with Extended Response Duration:				
≥6 months ≥12 months	38 (90.4) 29 (84.9)	19 (100.0) 13 (89.5)	9 (100.0) 8 (88.9)	12 (92.9) 10 (92.9)

Study: KEYNOTE-158	Endometrial (N=83)	Gastric (N=51)	Cholangio-carcinoma (N=22)	Small intestine (N=27)
≥18 months	16 (65.4)	12 (89.5)	6 (77.8)	9 (83.6)
≥24 months	13 (65.4)	10 (81.3)	4 (62.2)	7 (73.1)
≥36 months	11 (59.9)	8 (81.3)	2 (41.5)	7 (73.1)

[a] Includes participants with confirmed complete response or partial response.
[b] 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: 15OCT2021).

Endometrial

As of OCT-2021 data cutoff, median DOR was not reached (range: 2.9-60.4+ months, where “+” indicates an ongoing response as of the data cutoff date). By KM estimation, 59.9% of responders have an extended response duration of ≥36 months.

Gastric

As of OCT-2021 data cutoff, median DOR was not reached (range: 6.2-63.0+ months, where “+” indicates an ongoing response as of the data cutoff date). By KM estimation, 81.3% of responders have an extended response duration of ≥36 months.

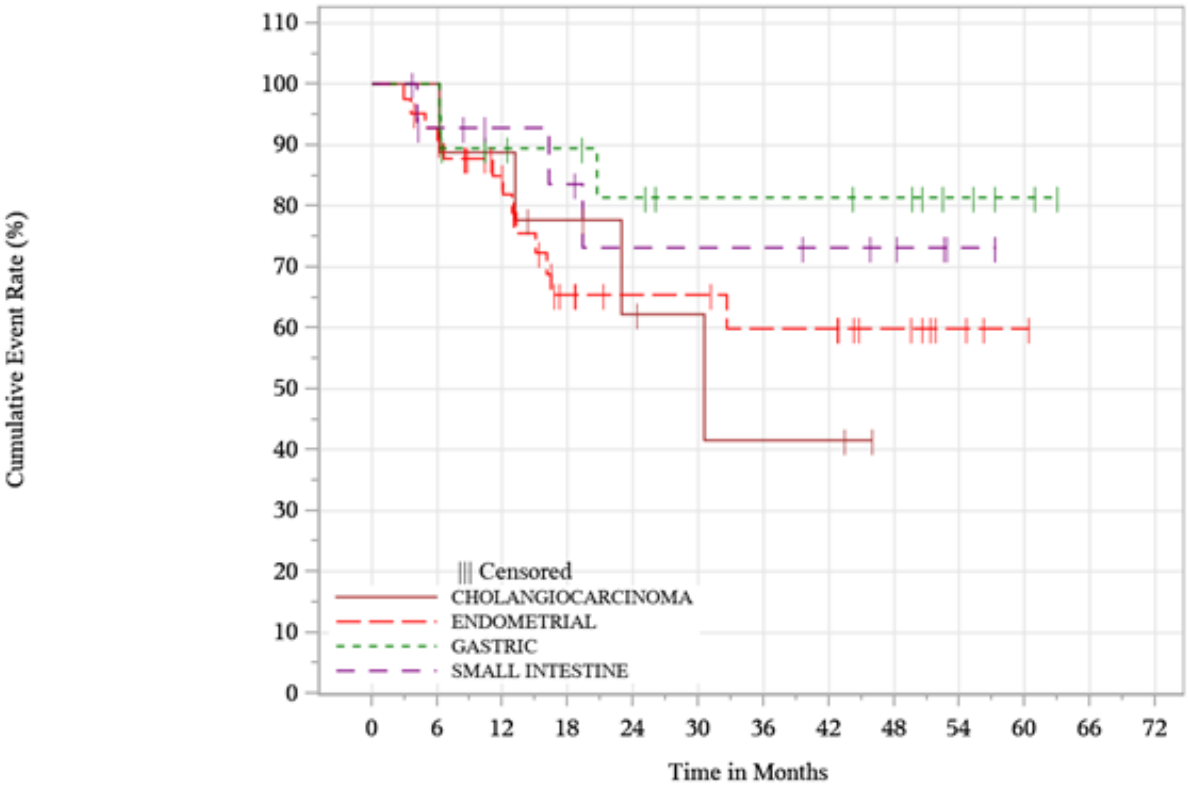
Small intestine

As of OCT-2021 data cutoff, median DOR was not reached (range: 3.7+ -57.3+ months, where “+” indicates an ongoing response as of the data cutoff date). By KM estimation, 73.1% of responders have an extended response duration of ≥36 months.

Biliary

As of OCT-2021 data cutoff, median DOR was 30.6 (range: 6.2 - 46.0+ months, where “+” indicates an ongoing response as of the data cutoff date). By KM estimation, 41.5% of responders have an extended response duration of ≥36 months.

Figure 8 KM estimates of objective response duration based on RECIST 1.1 per central radiology assessment in participants with confirmed response (ASaT population for efficacy analysis)



n at risk

CHOLANGIOCARCINOMA	9	9	8	6	4	3	2	2	0	0	0	0	0
ENDOMETRIAL	42	38	29	16	13	13	11	11	7	3	1	0	0
GASTRIC	19	19	13	12	10	8	8	8	7	4	2	0	0
SMALL INTESTINE	15	12	10	9	7	7	7	6	5	2	0	0	0

Notes: Database cutoff date: 15OCT2021.

B.2.6.2.3.2 Progression-free survival (PFS)

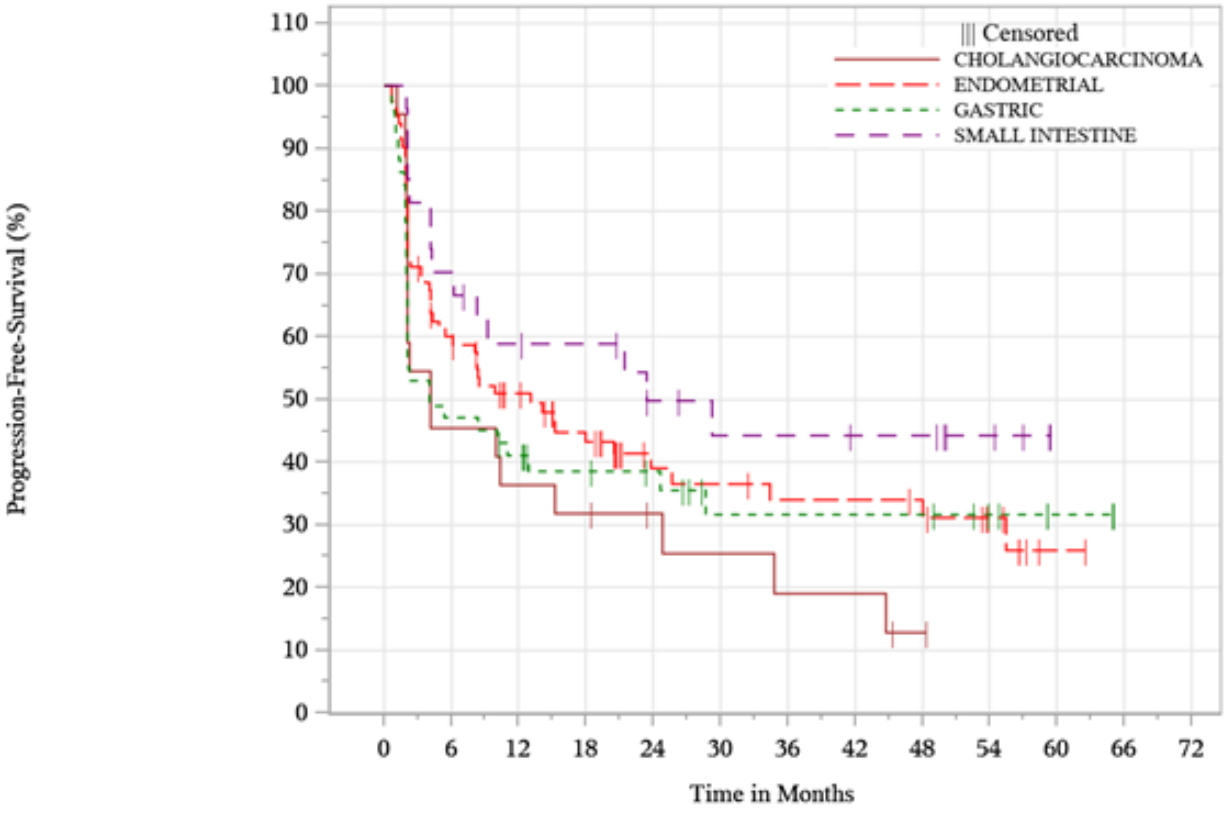
Table 24 shows PFS results by tumour site based on independent central radiologic review. Median PFS ranged from 4.1 (gastric) to 23.4 (small intestine) (Figure 9). At 24 months, more than 30% of participants in each tumour site had not progressed, by KM estimation.

Table 24 Summary of PFS based on RECIST 1.1 per central radiology assessment by tumour site (ASaT population for efficacy analysis)

Study: KEYNOTE-158	Endometrial (N=83)	Gastric (N=51)	Cholangiocarcinoma (N=22)	Small intestine (N=27)
Number (%) of PFS events	51 (61.4)	33 (64.7)	18 (81.8)	14 (51.9)
Person-months	1352	795	304	632
Event rate/100 person-months (%)	3.8	4.2	5.9	2.2
Median PFS (months)[a]	13.1	4.1	4.2	23.4
95% CI for median PFS[a]	(4.9, 25.7)	(2.1, 24.6)	(2.1, 24.9)	(4.3, NR)
PFS rate at 6 months in % [a]	60.0	47.1	45.5	70.4
PFS rate at 12 months in % [a]	50.9	41.1	36.4	58.8
PFS rate at 18 months in % [a]	44.8	38.5	31.8	58.8
PFS rate at 24 months in % [a]	39.0	38.5	31.8	49.8

Progression-free survival is defined as time from date of first dose to disease progression, or death, whichever occurs first; NR = Not reached
[a] From product-limit (Kaplan–Meier) method for censored data.
Participants who received at least one dose of pembrolizumab in KN158 with MSI-H tumours in cohort K with 6 months follow-up are included. (Database Cutoff Date: 15OCT2021).

Figure 9 KM estimates of PFS based on RECIST1.1 per central radiology assessment by tumour site (ASaT population for efficacy analysis)



n at risk

CHOLANGIOCARCINOMA	22	10	8	7	5	4	3	3	1	0	0	0	0
ENDOMETRIAL	83	48	36	28	16	15	13	13	12	7	1	0	0
GASTRIC	51	24	20	15	13	8	8	8	8	5	2	0	0
SMALL INTESTINE	27	19	15	14	10	8	8	7	7	4	0	0	0

Notes: Database cutoff date: 15OCT2021.

Endometrial

As of OCT-2021 data cutoff, events were observed in 51 (61.4%) participants. Median PFS was 13.1 months (95%CI: 4.9, 25.7) with 39% of participants being still progression-free at 24 months, by KM estimation.

Gastric

As of OCT-2021 data cutoff, events were observed in 33 (64.7%) participants. Median PFS was 4.1 months (95%CI: 2.1, 24.6) with 38.5% of participants being still progression-free at 24 months, by KM estimation.

Small intestine

As of OCT-2021 data cutoff, events were observed in 14 (51.9%) participants Median PFS was 23.4 months (95%CI: 4.3, NR) with 49.8% of participants being still progression-free at 24 months, by KM estimation.

Biliary

As of OCT-2021 data cutoff, events were observed in 18 (81.8%) participants. Median PFS was 4.2 months (95%CI: 2.1, 24.9) with 31.8% of participants being still progression-free at 24 months, by KM estimation.

B.2.6.2.3.3 Overall survival

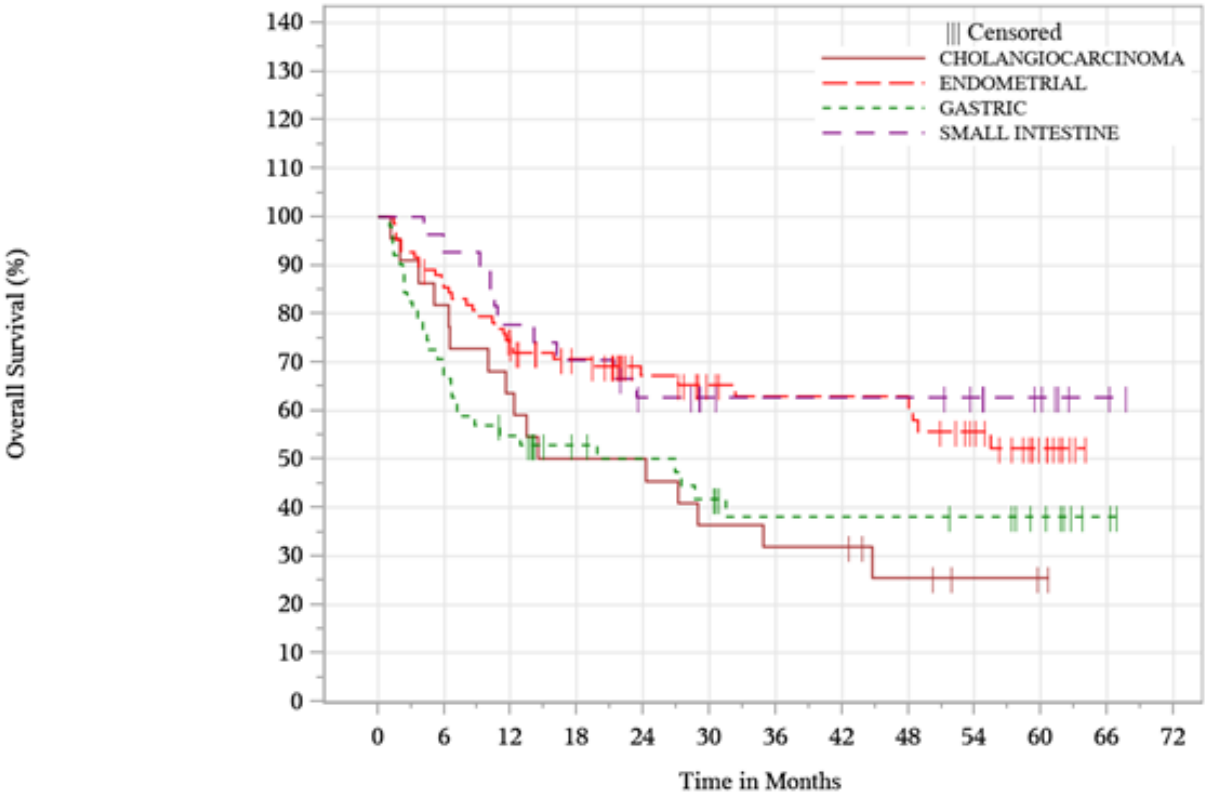
Treatment with pembrolizumab suggested a prolonged benefit with respect to OS. Median OS was not reached in two tumour sites (endometrial and small intestine) (Figure 10), and at 24 months OS rates were greater than or equal to 50% in each tumour site (Table 25).

Table 25 Summary of overall survival by tumour site (ASaT population for efficacy analysis)

Study: KEYNOTE-158	Endometrial (N=83)	Gastric (N=51)	Cholangiocarcinoma (N=22)	Small intestine (N=27)
Death (%)	32 (38.6)	29 (56.9)	16 (72.7)	10 (37.0)
Median survival (months)[a]	Not reached	26.9	19.4	Not reached
95% CI for median survival[a]	(48.0,NR)	(6.6,NR)	(6.5,44.8)	(16.2,NR)
OS rate at 6 months in % [a]	85.5	66.7	81.8	92.6
OS rate at 12 months in % [a]	73.3	54.8	63.6	77.8
OS rate at 18 months in % [a]	70.6	52.8	50.0	70.4
OS rate at 24 months in % [a]	67.2	50.0	50.0	62.7

OS: Overall survival.
[a] From product-limit (Kaplan–Meier) method for censored data.
Participants who received at least one dose of pembrolizumab in KN158 with MSI-H tumours in cohort K with 6 months follow-up are included. NR = Not reached.
(Database cutoff date: 15OCT2021).

Figure 10 KM estimates of overall survival by tumour site (ASaT population for efficacy analysis)



n at risk

CHOLANGIOCARCINOMA	22	18	14	11	11	8	7	7	4	2	1	0	0
ENDOMETRIAL	83	70	58	48	35	29	26	26	26	19	9	0	0
GASTRIC	51	34	27	20	18	15	11	11	11	10	7	2	0
SMALL INTESTINE	27	25	21	19	15	12	11	11	11	9	6	2	0

Notes: Database cutoff date: 15OCT2021.

Endometrial

As of OCT-2021 data cutoff, death events occurred in 32 (38.6%) participants. Median OS was not reached (95%CI: 48.0, NR) with 67.2% of participants being still alive at 24 months.

Gastric

As of OCT-2021 data cutoff, death events occurred in 29 (56.9%) participants. Median OS was 26.9 months (95%CI: 6.6,NR) with 50.0% of participants being still alive at 24 months.

Small intestine

As of OCT-2021 data cutoff, death events occurred in 10 (37.0%) participants. Median OS was not reached (95%CI: 16.2,NR) with 62.7% of participants being still alive at 24 months.

Biliary

As of OCT-2021 data cutoff, death events occurred in 16 (72.7%) participants. Median OS was 19.4 months (95%CI: 6.5,44.8) with 50.0% of participants being still alive at 24 months.

B.2.6.2.3.4 Patient-reported outcomes

No PROs were collected at the time of 15-OCT-2021 data cutoff. Data reported below were collected in previous data cutoff (05-OCT-2020 – IA11) and were pooled to include participants with the four tumour types from Cohort K relevant to this appraisal.

PROs were evaluated using the EORTC QLQ-C30 and the EQ-5D-3L questionnaires. The analysis for PROs is based on the full analysis set (FAS) population with both baseline and post-baseline measurements. The data are presented without imputation for missing data.

PRO analyses based on EORTC QLQ-C30 will be provided in Appendix N.

EQ-5D

Both the EQ-5D health utility score and VAS scores were measured. Completion rates were [redacted]% and [redacted]% at baseline and week 9, respectively. Compliance rates were [redacted]% and [redacted]% at baseline and week 9, respectively.

EQ-5D health utility score

At week 9, an improvement in the EQ-5D health utility score from baseline across all participants was observed (mean change = [redacted] points; 95% CI: [redacted]). Among participants who achieved CR/PR, analysis of the EQ-5D health utility score showed a [redacted] change from baseline with a mean change of [redacted] points (95% CI: [redacted]) (Table 26).

Table 26 Summary of mean change from baseline to Week 9 in EuroQol EQ-5D utility score (FAS population)

Endpoint	Treatment	N	Baseline	Week 9	Change from baseline to Week 9
			Mean (SD)	Mean (SD)	Mean (95% CI)
European utility value rescaled with the mean value for dead	All participants	[redacted]	[redacted]	[redacted]	[redacted]
	Participants who responded (CR+PR)	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with SD	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with PD	[redacted]	[redacted]	[redacted]	[redacted]

N is the number of participants in each treatment group with non-missing change from baseline at the specific time point.
Database Cutoff Date: 05OCT2020

EQ-5D VAS scores

EQ-5D VAS scores across all participants improved from baseline to Week 9 (mean change=[redacted]points; 95% CI: [redacted]). Among participants who achieved CR/PR, an improvement in EQ-5D VAS score was observed with a mean change from baseline of [redacted]points (95% CI: [redacted]) (Table 27). EQ-5D VAS score over time was stable or improved from baseline through Week 111 (Figure 11).

Table 27 Summary of mean change from baseline to Week 9 in EuroQol EQ-5D VAS (FAS population)

Endpoint	Treatment	N	Baseline	Week 9	Change from Baseline to Week 9
			Mean (SD)	Mean (SD)	Mean (95% CI)
EQ VAS score	All participants	[redacted]	[redacted]	[redacted]	[redacted]
	Participants who responded (CR+PR)	[redacted]	[redacted]	[redacted]	[redacted]

Endpoint	Treatment	N	Baseline	Week 9	Change from Baseline to Week 9
			Mean (SD)	Mean (SD)	Mean (95% CI)
	Participants with SD	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with PD	[redacted]	[redacted]	[redacted]	[redacted]
N is the number of participants in each treatment group with non-missing change from baseline at the specific time point. Database cutoff date: 05OCT2020					

Figure 11 Mean change from baseline and 95% CI for the EORTC EQ-5D VAS over time (FAS population)

B.2.6.3 KEYNOTE-158 trial (database cutoff date 12-JAN-2022)

An additional interim analysis was performed (IA14 - database cutoff date: 12-JAN-2022), corresponding to an additional 3-month follow-up, as a response to a Food and Drug Administration (FDA) request. Compared to 15-OCT-2021 data cutoff, [redacted] additional PFS event had occurred only (endometrial cancer subgroup) and [redacted] OS events ([redacted] in endometrial, [redacted] in gastric and [redacted] in biliary subgroup) were reported for the tumour sites relevant to this appraisal. [redacted] Overall, the results from latest data-cut are consistent with the results previously presented.

A summary results table comparing the results from the two data cutoff dates is provided below (Table 28).

Table 28 Summary of efficacy results from OCT-2021 and JAN-2022 data cutoff

	Database Cutoff Date (15-OCT-2021)	Database Cutoff Date (12-JAN-2022)
Endometrial		
ORR, % (95% CI)	50.6 (39.4, 61.8)	[redacted]
Number (%) of PFS events	51 (61.4)	
Median PFS, months (95% CI)	13.1 (4.9, 25.7)	
PFS rate, % at 24 Months	39.0	
Number (%) of OS events	32 (38.6)	
Median OS, months (95% CI)	NR (48.0, NR)	
OS rate, % at 24 Months	67.2	
Gastric		
ORR, % (95% CI)	37.3 (24.1, 51.9)	[redacted]
Number (%) of PFS events	33 (64.7)	
Median PFS, months (95% CI)	4.1 (2.1, 24.6)	
PFS rate, % at 24 Months	38.5	
Number (%) of OS events	29 (56.9)	
Median OS, months (95% CI)	26.9 (6.6, NR)	
OS rate, % at 24 Months	50.0	
Small intestine		
ORR, % (95% CI)	55.6 (35.3, 74.5)	[redacted]
Number (%) of PFS events	14 (51.9)	
Median PFS, months (95% CI)	23.4 (4.3, NR)	
PFS rate, % at 24 Months	49.8	
Number (%) of OS events	10 (37.0)	
Median OS, months (95% CI)	NR (16.2, NR)	
OS rate, % at 24 Months	62.7	
Biliary Cancer		
ORR, % (95% CI)	40.9 (20.7, 63.6)	[redacted]
Number (%) of PFS events	18 (81.8)	
Median PFS, months (95% CI)	4.2 (2.1, 24.9)	

	Database Cutoff Date (15-OCT-2021)	Database Cutoff Date (12-JAN-2022)
PFS rate, % at 24 Months	31.8	[redacted]
Number (%) of OS events	16 (72.7)	[redacted]
Median OS, months (95% CI)	19.4 (6.5, 44.8)	[redacted]
OS rate, % at 24 Months	50.0	[redacted]

B.2.7 Subgroup analysis

For the KEYNOTE-158 trial, efficacy analysis by tumour site has been provided in section B.2.6.

For the KEYNOTE-164 trial, no subgroup analysis was performed. Due to the small sample size and the inherent exploratory nature of subgroup analyses, no valid and reliable conclusions can be drawn about the effectiveness of the technology in subgroups.

B.2.8 Meta-analysis

Due to the identification of only one study evaluating the efficacy and safety of pembrolizumab for each of the relevant previously treated MSI-H/dMMR solid tumours (i.e., KEYNOTE-164 and KEYNOTE-158), no meta-analysis was performed.

B.2.9 Indirect and mixed treatment comparisons

In the absence of RCTs comparing the efficacy of pembrolizumab directly with that of standard of care (SoC), indirect treatment comparisons (ITCs) were explored to understand the relative treatment effect of pembrolizumab versus comparators of interest. ITCs without adjustment for confounders and effect modifiers were conducted based on Cox proportional hazards models for all comparators. Where the effective sample size was deemed sufficient, and sufficient data were available, a matching-adjusted indirect comparison (MAIC) was conducted in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.(46) Table 29 provides a summary of which methods were used for each comparator. Details on the unadjusted ITC and MAICs are provided in Sections B.2.9.1 and B.2.9.2, respectively, as well as in Appendices P and Q.

Both KN-158 and KN-164 are single-arm trials, which increases the complexity of assessing treatment efficacy against other relevant comparators, given that standard

techniques such as Bucher ITCs and network meta-analyses require a common comparator/anchor to estimate relative treatment effects.(47) It is acknowledged that head-to-head evidence would provide the most robust source of efficacy evidence; however, in a histology-independent setting, these are considered impractical and single-arm basket trials are widely used. This presents just one of the challenges associated with assessing evidence in these complex indications. With this in mind, it was necessary to consider unanchored methods for making these comparisons.

ITCs were conducted for both OS and PFS outcomes. Since there are no other approved therapies for multiple MSI-H/dMMR solid tumour sites, comparator efficacy data identified by the clinical SLR were compared with pembrolizumab data in the relevant tumour site only. Furthermore, except for paclitaxel in gastric cancer and paclitaxel/doxorubicin in endometrial, there were no published data available specifically in MSI-H/dMMR-specific populations. As such, data were instead selected only on their suitability as a clinically relevant comparator based on the respective tumour site and line of therapy; this is likely to result in conservative estimates of relative efficacy, as evidence suggests that MSI-H/dMMR patients may have worse outcomes compared to patients with MSS or pMMR disease.(22-24)

The final list of comparators for each tumour site reflects the prevailing clinical guidelines and those that have been validated by clinical experts or referenced as part of existing SoC in previous NICE appraisals (Table 29).(1) The list of comparators includes a pooled group of three regimens: FOLFIRI (folinic acid, fluorouracil and irinotecan), FOLFOX4 and FOLFOX6 (two different regimens of folinic acid, fluorouracil and oxaliplatin). This group is referred to as pooled FOLFOX/FOLFIRI. The pooled comparator was chosen for the CRC tumour site to maximize the relevant data. Grouping of different comparators was only permitted where there was sufficient clinical rationale for a class effect, meaning that UK clinical experts confirmed that they would not expect efficacy or safety outcomes to vary between individual regimens within each respective group.(1) The methods that were used to analyse and implement these grouped therapies are discussed below.

As explained previously, clinicians identified FOLFOX/FOLFIRI as the key comparator in small intestine but did not expect MSD to find any published evidence

concerning efficacy in this cancer. This was confirmed in the SLR, which only identified evidence for nab-paclitaxel (which is used in the cost-effectiveness analysis).

Table 29 Final comparators and associated studies – feasible ITC approaches

Tumour site	Comparator	Unadjusted ITC	MAIC	Included studies
CRC	Pooled FOLFOX/ FOLFIRI	X		Li et al. 2018(48) Giantonio et al. 2007(49) Cao et al. 2015(50) Moore et al. 2016(51) Xie et al. 2014(52)
	TAS-102	X		Yoshino et al. 2012(53) Mayer et al. 2015 (54) Xu et al. 2018 (55)
Endometrial	Chemotherapy (physician's choice of paclitaxel or doxorubicin)	X	X	Makker et al. 2022(56)
Gastric	FOLFIRI	X		Moehler et al. 2016(57) Sym et al. 2013 (58)
	Paclitaxel	X		Chao et al. 2021(59)
Small intestine	Nab-paclitaxel	X		Overman et al. 2018 (60)
Cholangiocarcinoma	mFOLFOX	X		Choi et al. 2021(61) Hwang et al. 2015(62) Kim et al. 2019(63)
	mFOLFIRI	X		Choi et al. 2021(61)

Abbreviations: CRC, colorectal cancer; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; (m)FOLFIRI, (modified) folinic acid, fluorouracil and irinotecan; mFOLFOX6, modified folinic acid, fluorouracil and oxaliplatin.

Full details of the methods used to explore unadjusted ITCs and MAICs are provided in the sections below and in Appendix P and Appendix Q, respectively. However, without exception, assessment of the log-cumulative hazards plots for each comparator indicated that the proportional hazards assumption was violated. This was anticipated due to the differing mechanisms of action between pembrolizumab and conventional chemotherapy, which result in different OS and PFS hazard profiles; specifically, pembrolizumab is associated with long-term survival benefits

and an established “functionally cured” group by around 5 years irrespective of tumour site (as validated by clinical experts). For this reason, the resulting HR estimates were considered inappropriate and were not investigated further within the cost-effectiveness analysis described in Section B.3.2.

Due to the small sample size available within each tumour site, it was not feasible to explore methods to generate time-varying HRs that do not rely on the proportional hazards assumption. Instead, separate parametric survival distributions were fitted to the available pseudo-individual patient data (IPD) for each comparator and are used within the economic analysis. The number of patients at risk over time alongside the digitized Kaplan-Meier curve from the published literature are used to derive pseudo-individual patient level data (IPD) using the method developed by Guyot et al. 2012(64) This approach of fitting separate parametric survival distributions does not require the proportional hazards assumption to hold. Furthermore, given that there was a negligible impact of adjusting for observed confounders, the impact of bias when using parametric curves fitted to unadjusted data is expected to be low, and substantially reduced compared to alternative methods – and, in the case of the chemotherapy comparator in the endometrial tumour site, use of unadjusted data may bias against pembrolizumab (OS unadjusted HR, 0.29; OS MAIC HR, 0.23).

B.2.9.1 Unadjusted ITCs

For each comparator, survival outcomes were extracted from the relevant publications and pseudo-IPD were generated by digitization, using methods described by Guyot et al. (2012) (64) To provide a meaningful comparison where there was more than one relevant study, pooled KM curves were derived to synthesize information across the studies. If only one study was used for comparison against pembrolizumab, KM curves were presented without pooling.

A summary of the outcomes of the unadjusted ITC, in the form of OS and PFS HRs, is presented by comparator and by tumour site in Table 30.

Table 30 OS and PFS HRs for pembrolizumab versus comparator therapies, by tumour site

Tumour site	Comparator	HR versus comparator (95% CI)	
		OS	PFS
CRC	TAS-102	0.26 (0.18; 0.38)	0.34 (0.25; 0.46)

Tumour site	Comparator	HR versus comparator (95% CI)	
		OS	PFS
	Pooled FOLFOX/FOLFIRI	0.30 (0.23; 0.39)	0.54 (0.43; 0.69)
Endometrial	Chemotherapy (physician's choice of paclitaxel or doxorubicin)	0.29 (0.18; 0.48)	0.39 (0.26; 0.60)
Gastric	FOLFIRI	0.40 (0.23; 0.71)	0.41 (0.24; 0.70)
	Paclitaxel	0.52 (0.25; 1.09)	0.73 (0.36; 1.51)
Small intestine	Nab-paclitaxel	0.18 (0.07; 0.45)	0.22 (0.09; 0.52)
Cholangiocarcinoma	mFOLFOX	0.30 (0.16; 0.58)	0.50 (0.27; 0.92)
	mFOLFIRI	0.27 (0.14; 0.54)	0.36 (0.18;0.71)

Abbreviations: CRC, colorectal cancer; CI, confidence interval; HR, hazard ratio; mFOLFIRI, modified folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; OS, overall survival; PFS, progression-free survival

The unadjusted ITC methods, study populations, KM data, and results are further described in Appendix P.

B.2.9.2 MAICs

If a sufficiently effective sample size was obtained after matching, an ITC with adjustment for confounders and effect modifiers was performed using an MAIC. MAIC enables the calculation of adjusted relative treatment effect estimates (e.g. HRs) in one direct step and allows weights to be derived from the chosen variables; the same set of weights can be used for all relevant outcome models (e.g. OS and PFS).(46) An MAIC was performed if two comparator arms were selected for a particular comparison, and if relevant information on confounders and effect modifiers was available for all included studies. The selected effect modifiers used were similar to those chosen in previous NICE appraisals in CRC (TA716)(28), endometrial cancer (NICE TA779)(31), and cholangiocarcinoma (NICE TA722).(65) As detailed in Appendix Q, MAICs were only possible in one case: physician's choice of paclitaxel or doxorubicin in endometrial cancer.

A summary of the MAIC methodology and results is provided below. Full details of the methods adopted for the MAIC are included in Appendix Q and follow NICE technical guidance.(46)

B.2.9.2.1 KN-158 MAIC

B.2.9.2.1.1 KN-158 MAIC methods

The following baseline characteristics, identified as potential effect modifiers and/or key prognostic factors based on clinical expertise, were selected as matching variables for both OS and PFS endpoints (Appendix Q):

- Age (median)
- Race (White, Black, Asian, other)
- Eastern Cooperative Oncology Group (ECOG) (0 vs 1)
- Number of prior lines of therapy (1 vs ≥2)
- Histology status (endometrioid carcinoma, others)

B.2.9.2.1.2 KN-158 MAIC results

Baseline characteristics

Selected key baseline characteristics are summarized in Table 31 for the comparison between pembrolizumab and physician's choice of paclitaxel or doxorubicin. For pembrolizumab (KN158) versus physician's choice (KN775), the effective sample size (ESS) after matching is 34.87, which is a reduction of 58% of the original sample size of 83.

Table 31 Baseline characteristics

	Physician's choice	Study: KEYNOTE 158[a]	
		Before matching	After matching
	(N[c]=65)	(N[b]=83)	(N=34.87[d])
Age			
Median	63.0	64.0	62.0
ECOG performance status (%)			
0	52.3	45.8	52.3
1	47.7	54.2	47.7
Race (%)			
White	53.8	84.3	53.8
Black	7.7	3.6	7.7
Asian	18.5	6.0	18.5
Other	20.0	6.0	20.0

	Physician's choice	Study: KEYNOTE 158[a]	
		Before matching	After matching
	(N[c]=65)	(N[b]=83)	(N=34.87[d])
Prior lines of therapy (%)			
1	78.5	53.0	78.5
≥2	21.5	47.0	21.5
Histology (%)			
Endometrioid carcinoma	86.2	65.1	86.2
Other	13.8	34.9	13.8

Abbreviations: ECOG, Eastern Cooperative Oncology Status.
a: Database Cutoff Date: 15OCT2021
b: Number of participants: Based on KEYNOTE 158, All-Participants-as-Treated population for efficacy analysis, Cohort K, MSI-H with Endometrial Carcinoma, at least one line of prior therapy
c: Number of participants: Based on Makker 2022
d: Effective sample size computed as the square of the summed weights divided by the sum of the squared weights; Weighted according to matched baseline characteristics of selected comparators Selected comparators: treatment of physician's choice (TPC) based on Makker 2022

Overall survival

The results of the OS analysis for the 'all subjects as treated' (ASaT) population are presented in Table 32, and the corresponding KM curve is presented in Figure 12. The outcomes both before and after matching show a statistically significant favourable HR (i.e. <1) towards pembrolizumab.

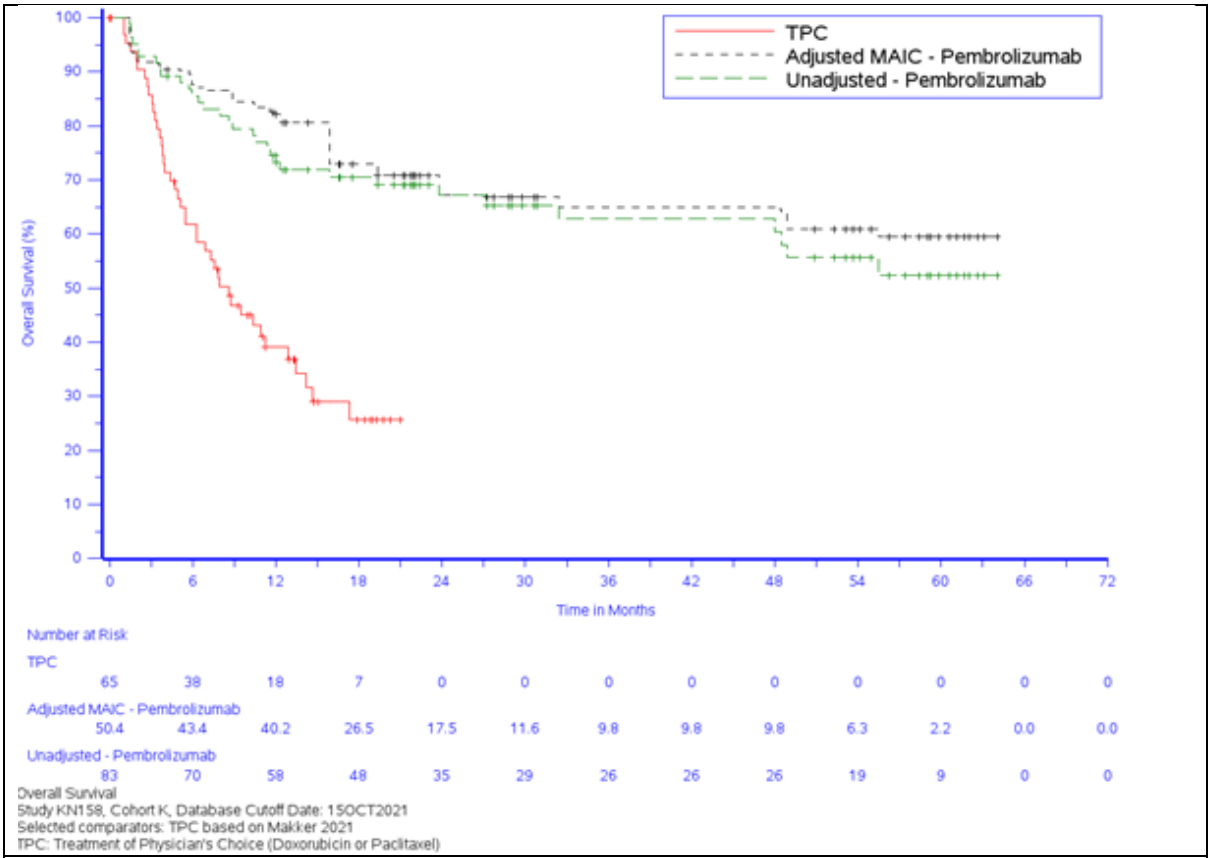
As detailed in Appendix Q, graphical investigation based on Schoenfeld residual plots and the log-cumulative hazard plots shows violation of the proportional hazards assumption, particularly after matching. Due to small sample size, no additional models for time-varying HRs were fitted.

Table 32 Analysis of overall survival

Study: KEYNOTE 158[a]	Pembrolizumab			Physician's choice			Pembrolizumab vs physician's choice	
	N[b]	Participants with event, n (%)	Median time[c] in months [95%-CI]	N[d]	Participants with event, n (%)	Median time[c] in months [95%-CI]	Hazard ratio [95%-CI][e]	p-value[e,f]
Before matching	83	32 (38.6)	Not reached [48.0; -]	65	42 (64.6)	8.6 [5.5; 12.9]	0.29 (0.17, 0.48)	< 0.001
After matching[g]	50.4[h]	16 (31.7)	Not reached [23.8; -]	65	42 (64.6)	8.6 [5.5; 12.9]	0.23 (0.12, 0.48)	< 0.001

Abbreviations: CI, confidence interval; MSI-H, microsatellite instability-high; TPC, treatment of physician's choice (doxorubicin or paclitaxel).
Notes:
a: Database cutoff date: 15OCT2021
b: Number of participants: Based on KEYNOTE 158, All-Participants-as-Treated population for efficacy analysis, Cohort K, MSI-H with Endometrial Carcinoma, at least one line of prior therapy
c: From product-limit (Kaplan–Meier) method for censored data
d: Number of participants: Based on Makker 2022
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Matching was done on the following covariates: Age (Median), ECOG Status, Race, Prior Lines of Therapy and Histology Status
h: Sample size after matching computed as the sum of the weights
Selected comparators: TPC based on Makker 2022.

Figure 12 KM curve for overall survival



Abbreviations: KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; TPC, treatment of physicians' choice (doxorubicin or paclitaxel).

Progression-free survival

The results of the PFS analysis for the ASaT population are presented in Table 33, and the corresponding KM curves are presented in Figure 13. As for OS, the outcomes both before and after matching show a statistically significant favourable HR (i.e. <1) towards pembrolizumab.

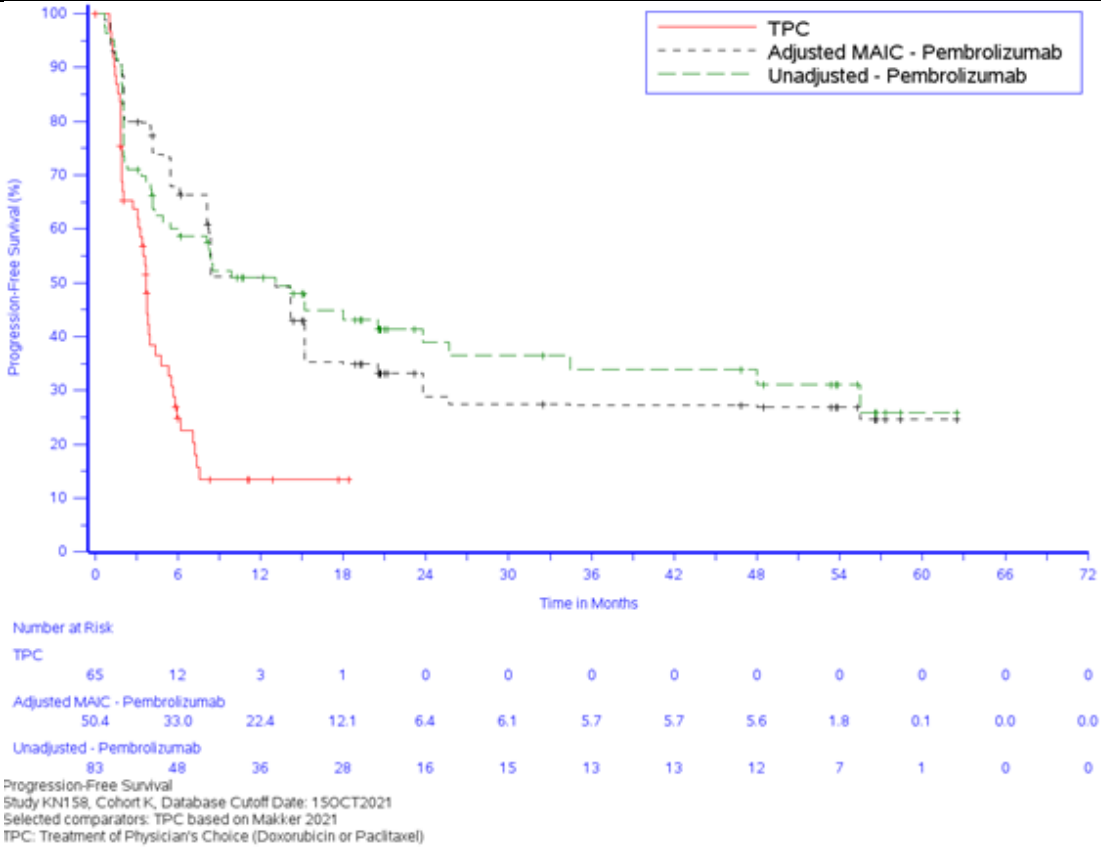
As detailed in Appendix Q, graphical investigation based on Schoenfeld residual plots and the log-cumulative hazard plots shows violation of the proportional hazards assumption, both before and after matching. Due to the small sample size, no methods that allow for time-varying HRs were considered.

Table 33 Analysis of progression-free survival

Study: KEYNOTE 158[a]	Pembrolizumab			Physician's choice			Pembrolizumab vs physician's choice	
	N[b]	Participants with event, n (%)	Median time[c] in months [95%-CI]	N[d]	Participants with event, n (%)	Median time[c] in months [95%-CI]	Hazard ratio [95%-CI][e]	p-value[e,f]
Before matching	83	51 (61.4)	13.1 [4.9; 25.7]	65	48 (73.8)	3.7 [3.1; 4.4]	0.40 (0.26, 0.62)	< 0.001
After matching[g]	50.4[h]	32 (63.5)	13.1 [5.5; 20.5]	65	48 (73.8)	3.7 [3.1; 4.4]	0.35 (0.20, 0.59)	< 0.001

Abbreviations: CI, confidence interval; MSI-H, microsatellite instability-high; TPC, treatment of physician's choice (doxorubicin or paclitaxel).
Notes:
a: Database Cutoff Date: 15OCT2021
b: Number of participants: Based on KEYNOTE 158, All-Participants-as-Treated population for efficacy analysis, Cohort K, MSI-H with Endometrial Carcinoma, at least one line of prior therapy
c: From product-limit (Kaplan–Meier) method for censored data
d: Number of participants: Based on Makker 2022
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Matching was done on the following covariates: Age (Median), ECOG Status, Race, Prior Lines of Therapy and Histology Status
h: Sample size after matching computed as the sum of the weights
Selected comparators: TPC based on Makker 2022

Figure 13 KM curve for progression-free survival



Abbreviations: KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; TPC, treatment of physicians' choice (doxorubicin or paclitaxel).

B.2.9.3 Uncertainties in the indirect comparisons

As raised previously, a key limitation of these indirect comparisons is that the proportional hazards assumption was violated. Consequently, estimates of comparative effectiveness derived by applying HRs to extrapolated pembrolizumab outcomes are inappropriate.

The MAIC follows the recommendations in NICE DSU TSD 18(46), which states: 'for an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables'. Where possible, differences in patient characteristics were adjusted for to reduce bias; however, it was not possible to match for all characteristics given the substantial heterogeneity between KN-158 and comparator studies. The key modifier was MSI-H/dMMR status, which could not be adjusted for in any potential MAICs involving MSI-unselected sources given the

lack of baseline reporting. For the MAIC conducted versus treatment of physician's choice (TPC) in endometrial cancer, MSI-H/dMMR status could not bias results given that patients were selected based on status.

Unanchored MAICs will also always be subject to unknown amounts of residual bias due to unobserved prognostic variables and effect modifiers. Furthermore, it was not possible to adjust comparator studies for the potential impact of MSI-H/dMMR status. This, combined with the small population sizes for some tumour sites in KN-158 and the lack of reported data for comparators, meant that MAICs were infeasible in most cases. However, failing to adjust for MSI-H/dMMR is likely to result in conservative estimates of relative efficacy, as evidence suggests that patients with MSI-H/dMMR disease may have worse outcomes compared to patients with MSS or pMMR disease(22-24), and should be taken into consideration when interpreting the modelled comparator outcomes. Consulted clinicians agreed that MSI-H/dMMR status is a potential negative prognostic variable, but emphasized that MSI-H/dMMR status is at least a treatment effect modifier for immunotherapies (i.e., they will be more efficacious in MSI-H/dMMR patients other things being equal).

Given the limitations and potential bias of the unadjusted ITCs and unanchored MAICs, neither were used further in the economic analyses. Therefore, parametric survival distributions were fitted to the comparator pseudo-IPD with the most clinically plausible extrapolation chosen for use in the base case. While it is acknowledged that this method is not ideal, it was considered the most reasonable in light of the evidence and potential bias introduced from other tested methods. These methods are described in Section B.3.2.1.

B.2.10 Adverse reactions

Summary of adverse events information

- The safety results from the KEYNOTE-164 and KEYNOTE-158 trials demonstrate that pembrolizumab is well tolerated in participants with dMMR or MSI-H across the five tumour sites.
- The overall number, type, and frequency of AEs and serious adverse events (SAE) reported are generally consistent with the well-known safety profile of pembrolizumab

monotherapy and the underlying diagnosis of dMMR or MSI-H metastatic solid tumours.

- [redacted] ([redacted]%) and [redacted] ([redacted]%) participants had at least 1 AE of any grade regardless of relationship to study intervention in the KEYNOTE164 and KEYNOTE 158 trials, respectively. The majority of these events were Grade 1 or 2 in severity.
- In KEYNOTE-164 trial, [redacted] of the [redacted] deaths were assessed as related to study treatment by the investigator. In KEYNOTE-158 trial, [redacted] ([redacted]%) participants had an AE that resulted in death but only [redacted] were reported to be drug-related.
- The most frequently reported AEOSI (≥4% of participants) in both trials were hypothyroidism and hyperthyroidism. There were [redacted] Grade 4 or 5 AEOSI reported in the KEYNOTE-164 trial.

B.2.10.1 KEYNOTE-164 trial (colorectal cancer)

B.2.10.1.1 Extent of exposure

The median duration of exposure to pembrolizumab was [redacted] weeks (range: [redacted] to [redacted] weeks), and the median number of administrations was [redacted] (range: [redacted] to [redacted]) (Appendix F).

B.2.10.1.2 Summary of adverse events

AEs as observed at FA (data cutoff date of 19-FEB-2021) are provided in this section. Further details of AEs are available in Appendix F.

Among the participants included in the ASaT population, [redacted] participants had at least 1 AE of any grade regardless of relationship to study intervention. [redacted] participants experienced a Grade 3 to 5 AE related to study intervention and [redacted] participants discontinued from study intervention due to an AE related to study intervention (Table 34).

Table 34 Adverse event summary (Pooled Cohorts A and B, ASaT population)

Study: KEYNOTE-164	Pembrolizumab 200 mg Q3W n (%)
Participants in population	[redacted]
with one or more adverse events	[redacted]
with no adverse event	[redacted]
with drug-related† adverse events	[redacted]
with toxicity grade 3-5 adverse events	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]
with serious adverse events	[redacted]
with serious drug-related adverse events	[redacted]
who died	[redacted]
who died due to a drug-related adverse event	[redacted]
discontinued‡ due to an adverse event	[redacted]
discontinued due to a drug-related adverse event	[redacted]
discontinued due to a serious adverse event	[redacted]
discontinued due to a serious drug-related adverse event	[redacted]

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each participant will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 19FEB2021

B.2.10.1.3 Most frequently reported adverse events

The most frequently reported AEs (incidence ≥20%) were fatigue, diarrhoea, nausea, abdominal pain, vomiting, arthralgia, pyrexia and constipation (Table 35). The majority of these events were Grade 1 or 2 in severity.

Table 35 Participants with adverse events by decreasing incidence (incidence ≥10%) (Pooled Cohorts A and B, ASaT population)

Study: KEYNOTE-164	Pembrolizumab 200 mg Q3W n (%)
Participants in population	[redacted]
with one or more adverse events	[redacted]
with no adverse events	[redacted]
	[redacted]
Fatigue	[redacted]
Diarrhoea	[redacted]
Nausea	[redacted]
Abdominal pain	[redacted]

Study: KEYNOTE-164	Pembrolizumab 200 mg Q3W	
Vomiting	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each participant will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
Database Cutoff Date: 19FEB2021

B.2.10.1.4 Grade 3 to 5 adverse events

Overall, [redacted] of participants reported at least 1 Grade 3 to 5 AE. The most frequently reported Grade 3 to 5 AEs (≥4% of participants) were anaemia, abdominal pain, alanine aminotransferase and aspartate aminotransferase increased, dyspnoea and sepsis (Appendix F).

B.2.10.1.5 Grade 3-5 drug-related adverse events

A total of [redacted] participants ([redacted]) reported at least 1 drug-related Grade 3-5 AE. The most frequently reported drug-related Grade 3-5 AEs (≥2 participants) were alanine aminotransferase increased, fatigue, lipase increased, and pancreatitis ([redacted] participants each) (Appendix F).

B.2.10.1.6 Deaths due to adverse events and other serious adverse events

[redacted] participants died due to AEs; these events were assessed as not related to study treatment by the investigator (Appendix F). [redacted] of participants reported at least 1 serious adverse event (SAE) (Appendix F).

B.2.10.1.7 Adverse events of special interest (AEOSI)

[redacted] participants reported at least 1 AEOSI. The most frequently reported AEOSI (≥4% of participants) were hypothyroidism, hyperthyroidism and pneumonitis. [redacted] participants reported Grade 3-5 AEOSI of which [redacted] were assessed by the investigator as related to study treatment. [redacted] participants reported SAEs of which [redacted] were assessed as related to study treatment (Table 36). There were [redacted] Grade 4-5 AEOSI and no participants died due to an AEOSI (Appendix F).

Table 36 Adverse event summary AEOSI (Pooled Cohorts A and B, ASaT population)

Study: KEYNOTE-164	**Pembrolizumab 200 mg Q3W**	
	n	**(%)**
Participants in population	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]
with drug-related† adverse events	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]
who died	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]
discontinued‡ due to an adverse event	[redacted]	[redacted]
discontinued due to a drug-related adverse event	[redacted]	[redacted]
discontinued due to a serious adverse event	[redacted]	[redacted]
discontinued due to a serious drug-related adverse event	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
After the end of treatment, each participant will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
AEs of special interest per ECI guidance.
Grades are based on NCI CTCAE version 4.0.
Database Cutoff Date: 19FEB2021

B.2.10.2 KEYNOTE-158 trial

B.2.10.2.1 Extent of exposure

Tables reporting median duration of exposure and median number of administrations are provided in Appendix F.

B.2.10.2.1.1 Endometrial

The median duration of exposure to pembrolizumab was [redacted] weeks (range: [redacted] to [redacted] weeks), and the median number of administrations was [redacted] (range: [redacted] to [redacted]) (Appendix F).

B.2.10.2.1.2 Gastric

The median duration of exposure to pembrolizumab was [redacted] weeks (range: [redacted] to [redacted] weeks), and the median number of administrations was [redacted] (range: [redacted] to [redacted]) (Appendix F).

B.2.10.2.1.3 Small intestine

The median duration of exposure to pembrolizumab was [redacted] weeks (range: [redacted] to [redacted] weeks), and the median number of administrations was [redacted] (range: [redacted] to [redacted]) (Appendix F).

B.2.10.2.1.4 Biliary

The median duration of exposure to pembrolizumab was [redacted] weeks (range: [redacted] to [redacted] weeks), and the median number of administrations was [redacted] (range: [redacted] to [redacted]) (Appendix F).

B.2.10.2.2 Summary of adverse events

AEs as observed at the latest data-cut (data cutoff date of 12-JAN-2022) for the population in Cohort K in the four tumour sites relevant for this appraisal (endometrial, gastric, small intestine and biliary), are provided in this section. Further details of AEs are available in Appendix F.

Among the participants who had at least 1 dose of pembrolizumab [redacted] ([redacted]%) participants had at least 1 AE of any grade regardless of relationship to study intervention. [redacted] ([redacted]%) participants experienced a Grade 3 to 5 AE related to study

intervention and [redacted] ([redacted]%) participants discontinued from study intervention due to an AE related to study intervention (Table 37).

Table 37 Adverse event summary (ASaT population)

Study: KEYNOTE-158	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]
with drug-related[a] adverse events	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]
who died	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]

[a] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
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: 12JAN2022).

B.2.10.2.3 Most frequently reported adverse events

The most frequently reported AEs (incidence ≥20%) were diarrhoea, fatigue, pruritus, arthralgia, nausea and vomiting (Table 38). The majority of these events were Grade 1 or 2 in severity.

Table 38 Participants with adverse events by decreasing incidence (incidence ≥ 10%) (ASaT population)

Study: KEYNOTE-158	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
	[redacted]	[redacted]

Study: KEYNOTE-158	Pembrolizumab 200 mg Q3W	
	n	(%)
Diarrhoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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: 12JAN2022).

B.2.10.2.4 Drug-related adverse events

Per investigator assessment, [redacted]% of participants had 1 or more AEs that was related to pembrolizumab. The majority of these events were Grade 1 or 2 in severity. The most frequently reported drug-related AEs (≥10%) were pruritus, fatigue, diarrhoea, arthralgia, rash, and hypothyroidism (Appendix F).

B.2.10.2.5 Grade 3 to 5 adverse events

A total of [redacted] ([redacted]%) participants had one or more Grade 3 to 5 AEs. The most frequently reported (≥2%) Grade 3 to 5 AEs were anaemia, blood alkaline phosphatase increased, aspartate aminotransferase increased, hyperglycaemia, and transaminases increased (Appendix F). These events were consistent with the

established safety profile of pembrolizumab monotherapy and with the underlying malignancies in patients with MSI-H tumours.

Per investigator assessment, [redacted] ([redacted]%) participants had 1 or more Grade 3 to 5 AEs that was related to study intervention (Appendix F).

B.2.10.2.6 Deaths due to adverse events

[redacted] ([redacted]%) participants had an AE that resulted in death. [redacted] participants cardiac failure, and [redacted] participant each had Guillain-Barre syndrome, general physical health deterioration, malabsorption, myocarditis, and pneumonia (Appendix F). Per investigator assessment, [redacted] deaths were reported to be drug-related.

B.2.10.2.7 Other serious adverse events

[redacted] ([redacted]%) participants had 1 or more SAEs. The most frequently reported SAEs were cholangitis and sepsis. Additional SAEs occurring at ≥1 % incidence are provided in Appendix F. Per investigator assessment, a total of [redacted] ([redacted]%) participants had 1 or more drug-related SAEs that occurred up to 90 days after the last dose of pembrolizumab (Appendix F).

B.2.10.2.8 Adverse events of special interest (AEOSI)

Overall, [redacted]% of participants had at least 1 AEOSI (Table 39) and [redacted]% had at least 1 drug-related AEOSI. Most AEOSI were nonserious and manageable with standard clinical practice measures, such as systemic corticosteroids or hormone replacement and/or treatment interruption. The most frequently reported AEOSI (>1%) were hypothyroidism, hyperthyroidism, colitis, pneumonitis, hepatitis, infusion-related reaction, Guillain-Barre syndrome and interstitial lung disease (Appendix F).

Table 39 Adverse event summary AEOSI (ASaT population)

Study: KEYNOTE-158	Pembrolizumab 200mg Q3W	
	n	(%)
Participants in population	[redacted]	[redacted]
with one or more adverse events	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]
with drug-related[a] adverse events	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]

Study: KEYNOTE-158	Pembrolizumab 200mg Q3W	
	n	(%)
with serious drug-related adverse events	[redacted]	[redacted]
who died	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]

[a] Determined by the investigator to be related to the drug.
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: 12JAN2022).

B.2.11 Ongoing studies

KEYNOTE-164 is completed. Results from FA are presented in section B.2.6.

KEYNOTE-158 is still ongoing as additional patients will be recruited. [redacted]. Further analysis for Cohort K will be conducted to meet regulatory requirements. However, timelines are currently unknown.

B.2.12 Interpretation of clinical effectiveness and safety evidence

KEYNOTE-158 and KEYNOTE-164 have evaluated the treatment effect of pembrolizumab in patients with previously treated unresectable and/or metastatic MSI-H or dMMR solid tumours. Patients at this advanced stage of cancer have typically a very poor life expectancy (less than a year from diagnosis); also, patients with MSI-H or dMMR solid tumours do not have targeted treatment options.

Based on the primary outcome of the two trials, more than 30% of the patients in each tumour site achieved a tumour response (ORR range: 33.9% - 55.6%) when treated with pembrolizumab. Median DOR was not reached in any of the tumour sites, except for biliary cancer. Among patients with tumour response, more than 40% in each tumour site experienced an extended response for ≥36 months. A

disease control of >50% in each tumour site was also reported. These results demonstrate that treatment with pembrolizumab can provide a clinically meaningful benefit to patients with respect to ORR, with durable responses.

The trials reported a median PFS ranging from 4 to 23.4 months with more than 30% of participants in any tumour sites that had not progressed at 24 months. Median OS ranged from 19.4 to 36.1 months (median OS was not reached in two tumour sites) and more than 50% of participants in each tumour type treated with pembrolizumab were still alive at 24 months.

In the absence of RCTs, unadjusted ITCs and MAICs, where feasible, were explored to compare the treatment effect of pembrolizumab with that of comparators of interest in line with the decision problem. With both comparison methods, pembrolizumab was associated with an improvement in PFS and OS compared to relevant comparators. It was only possible to conduct a MAIC in endometrial cancer against physician's choice of paclitaxel or doxorubicin. This showed a statistically significant favourable HR (i.e., <1) towards pembrolizumab.
While noting the limited knowledge of the prognostic significance of MSI-H/dMMR status for each tumour site, it is reasonable to assume that these comparisons with comparators of interest from unselected MSI-H population are conservative and therefore better efficacy outcomes for pembrolizumab can be expected if comparison was carried out within the MSI-H/dMMR population.
However, with the anticipated violation of the proportional hazards assumption and given that no additional models for time-varying HRs could be explored, the resulting HR estimates were considered inappropriate and were not investigated further within the cost-effectiveness analysis.

Overall, treatment with pembrolizumab was well tolerated in participants with MSI-H or dMMR across the five tumour sites. The safety outcomes were generally consistent with the well-known safety profile of pembrolizumab monotherapy and the underlying diagnosis of MSI-H or dMMR metastatic solid tumours. Most AEOSI were nonserious and manageable with standard clinical practice measures, such as systemic corticosteroids or hormone replacement and/or treatment interruption.

Internal validity

- Objective response rate, the primary endpoint in the KEYNOTE-158 and KEYNOTE-164 trials, as well as progression-free survival, a secondary endpoint, were assessed by independent central radiologic review, which ensured an unbiased and consistent evaluation of imaging across the trial centres.

- Given the rarity of most of the cancers investigated, the KEYNOTE-158 trial remained open to allow the additional recruitment of patients and obtain a sufficiently large cohort for a more precise assessment of the clinical activity of pembrolizumab in MSI-H advanced solid tumours. More than twenty participants have been recruited in each of the tumour sites relevant to this appraisal including biliary and small intestine cancers.

External validity

The results of the KEYNOTE-158 and KEYNOTE-164 trials can be considered generalizable to the clinical practice in the UK. The trials' population broadly reflects the characteristics of the population in each of the five tumour sites in the UK. The outcomes evaluated in both trials are in line with the NICE scope as relevant to both patients and clinicians. The comparators selected from the studies identified with the SLR for each tumour site, where evidence was available, and used in the ITCs, include therapies currently recommended by NICE, and those identified by clinical experts as current standard of care.

One limitation of the evidence informing this appraisal is related to the non-randomized nature of both studies (single-arm trials) that prevented head-to-head comparisons with comparators that reflect current clinical practice. This was due to the rarity of most of the cancers in these trials, and the low prevalence of MSI-H/dMMR within these tumours, as well as the difference in comparators across the tumour sites.

Attempts to overcome this limitation were made by exploring ITC methods. While acknowledging the limitations of this type of comparisons (e.g., unadjustment for unobserved confounders, small sample size and lack of data preventing MAICs) as well as the violation of proportional hazard in all the comparisons, it is important to note that the PFS and OS results consistently favoured pembrolizumab across all

comparisons (HRs were equal to or lower than 0.73 and 0.52 for PFS and OS, respectively, across all comparisons).

Within the KEYNOTE-158/164 trials, the sample size was small for most of the tumour sites which resulted in less precise results and larger confidence intervals. Subgroup analysis within these populations could not be conducted as the size, along with the inherent exploratory nature of subgroup analyses, would not enable valid and reliable conclusions to be drawn about the effectiveness of the technology in subgroups.

Overall, clinically relevant benefits associated with pembrolizumab have been observed across all five tumour sites evaluated in this appraisal which, despite the heterogeneity across histologies, is suggestive of MSI-H status being predictive of increased activity relative to non MSI-H tumours of the same origin, in relation to checkpoint inhibitors like pembrolizumab. This was also noted by the CHMP in the context of the regulatory evaluation of this indication, which confirmed the positive predictive value of the MSI status for the approved indications.(4)
This is particularly important considering the poorer survival outcomes with which MSI-H/dMMR cancers are known to be potentially associated at later stages of the disease. Consulted clinical experts agreed that MSI-H/dMMR is potentially a negative prognostic factor, but emphasized that MSI-H/dMMR status is at least a treatment effect modifier for immunotherapies (i.e. they will be more efficacious in MSI-H/dMMR patients other things being equal).(1) While the KEYNOTE-158 trial cohort K also includes MSI-H/dMMR tumours with other histologies, the four tumour sites for which the marketing authorization was pursued (endometrial, gastric, small intestine and biliary cancers) have been chosen based on a combination of factors including unmet need and antitumour activity observed with anti-PD-1 immunotherapy.

The outcomes summarized above can positively impact patients with MSI-H or dMMR solid tumours who currently do not have targeted treatment options and can only be offered subsequent chemotherapies after first-line chemotherapies have failed.

B.3 Cost-effectiveness

B.3.1 Published cost-effectiveness studies

A SLR was conducted in July 2021 to identify relevant published economic evidence in second-line or later settings to treat MSI-H/dMMR advanced/metastatic solid tumours. At the time of this submission, pembrolizumab was the only approved therapy for MSI-H/dMMR solid tumours; therefore, it was expected there would be a paucity of evidence in this specific population. To proactively overcome this, the search strategies used were not restricted to studies conducted in MSI-H/dMMR-specific populations, or to studies that included more than one tumour site, as the aim was to return the greatest number of relevant included studies possible. Studies with MSI-H/dMMR specific populations were prioritized for data extraction, although no studies in this population reported on interventions for multiple tumour sites. Full details of these searches and the findings are reported in Appendix G.

In addition to the full SLR conducted in July 2021, a subsequent targeted literature review was conducted in August 2022 to ensure that, at the time of submission, all relevant previous cost-effectiveness studies were identified. This search was restricted to multi-cohort cost-effectiveness analysis studies conducted in MSI-H/dMMR tumours for the specific tumour sites of interest (aligned with the decision problem) and was used to identify relevant cost-effectiveness studies only. As detailed in Appendix G, no studies were identified.

The final step was to identify and review relevant NICE appraisals. No NICE appraisals were identified for tumour site-independent treatments in the specific population of interest in this submission; therefore, the following searches were performed:

- Review of NICE appraisals of histology-independent therapies, irrespective of disease area
- Review of NICE appraisals of therapies used in patients with previously treated cancer, for each of the tumour sites of interest (i.e. colorectal, endometrial, gastric, small intestine and cholangiocarcinoma)

From these NICE searches, two appraisals were identified for histology independent therapies, and nine were identified in the tumour sites of interest (four for CRC, three for gastric cancer, one for endometrial cancer and one for biliary cancer). The results of the NICE appraisal review are summarized in Appendix G and were used to inform the approach to the economic evaluation described throughout the remainder of Section B.3.

B.3.2 Economic analysis

A cost-effectiveness analysis was undertaken from the perspective of the NHS, comparing pembrolizumab with existing SoC in the five relevant tumour sites for previously treated MSI-H/dMMR solid tumours. A multi-cohort partitioned survival model was developed, evaluating outcomes in each tumour site separately before combining to estimate overall cost-effectiveness results based on the distribution of patients between different tumour sites. The model uses a lifetime time horizon and a discount rate of 3.5% for cost and health outcomes, as requested by the current NICE reference case.

This economic evaluation adheres to the methodological requirements set out in the updated NICE health technology evaluations manual published January 2022. Importantly, analyses presented in Section B.3.6 demonstrate that pembrolizumab is eligible for a severity-of-disease decision modifier, with the quality-adjusted life year (QALY) weight varying by tumour site based on the current prognosis and level of unmet need. Analyses indicate colorectal and endometrial tumour sites qualify for a QALY weight of 1.2, while the remaining tumour sites (gastric, small intestine, biliary) are eligible for a QALY weight of 1.7.

B.3.2.1 Patient population

The modelled patient population for MSI-H/dMMR solid tumours reflects the final NICE scope and the approved MHRA and EMA label for pembrolizumab as monotherapy for the treatment of the following MSI-H or dMMR tumours in adults:

- Unresectable or metastatic colorectal cancer (mCRC) after previous fluoropyrimidine-based combination therapy

- Advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation

- Unresectable or metastatic gastric cancer, small intestine cancer or biliary cancer, who have disease progression on or following at least one prior therapy

This is consistent with the patient populations included in KN-164 and KN-158 (Cohort K) and corresponds to the five tumour sites of interest that are included in the cost-effectiveness analysis and are summarized as:

- Colorectal (KN164)

- Endometrial (KN158)

- Gastric (KN158)

- Small intestine (KN158)

- Cholangiocarcinoma (biliary cancer, KN158)

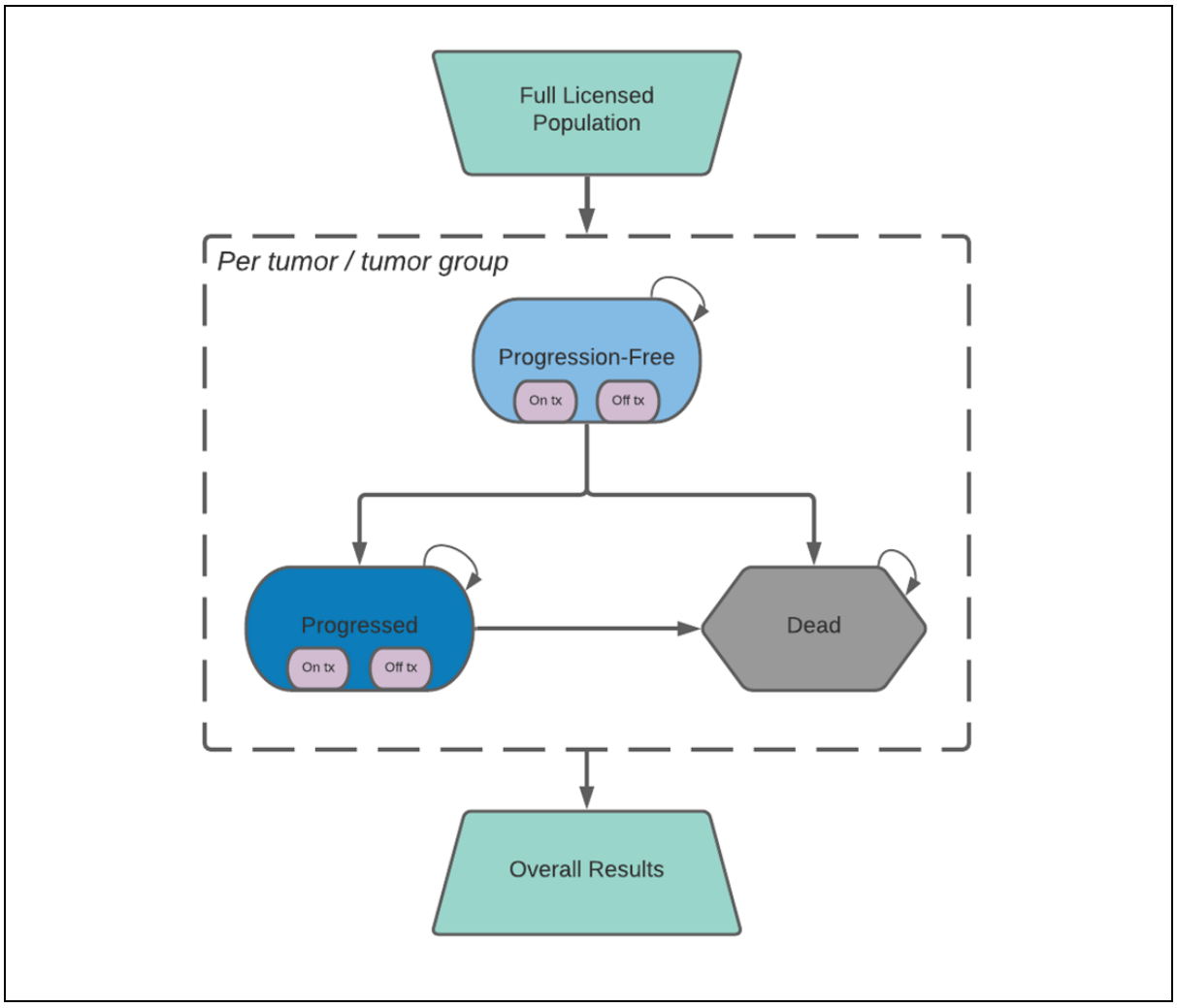
When comparing baseline characteristics of patients enrolled in KN-158 and KN-164 with those in the comparator studies, notable differences include MSI-H/dMMR status and disease stage. With the exception of paclitaxel in gastric cancer and TPC (paclitaxel/doxorubicin) in endometrial, patients in comparator studies were not selected by MSI-H/dMMR status. As noted in Section B.2.8, where comparator populations are not specific to patients with MSI-H/dMMR tumours, this is likely to result in conservative estimates of relative effectiveness for pembrolizumab, given MSI-H/dMMR status is associated with a poorer prognosis.(22-24) Disease stage is also a prognostic indicator(27); however, this characteristic was rarely reported for comparators. In KN-164, only patients with Stage IV disease were included (Table 10), which therefore may also bias outcomes against pembrolizumab in the CRC setting, as comparator studies did not specify this inclusion criterion.

Overall, clinicians indicated that the populations observed in KN-158 and KN-164 were generalizable to UK clinical practice.(1) Patient characteristics for each comparator study are included in Appendix P and Q.

B.3.2.2 Model structure

As no economic evaluations have previously been reported which align with the decision problem, a de novo multi-cohort partitioned survival model was developed to determine the cost-effectiveness of pembrolizumab versus relevant comparators for the treatment of patients with MSI-H/dMMR solid tumours. The model structure is presented in Figure 14. As presented in the multi-cohort structure, each tumour site is modelled separately and then aggregated to generate outcomes across all tumour sites, weighted by the tumour site prevalence described in Table 43.

Figure 14 Multi-cohort cost-effectiveness model structure

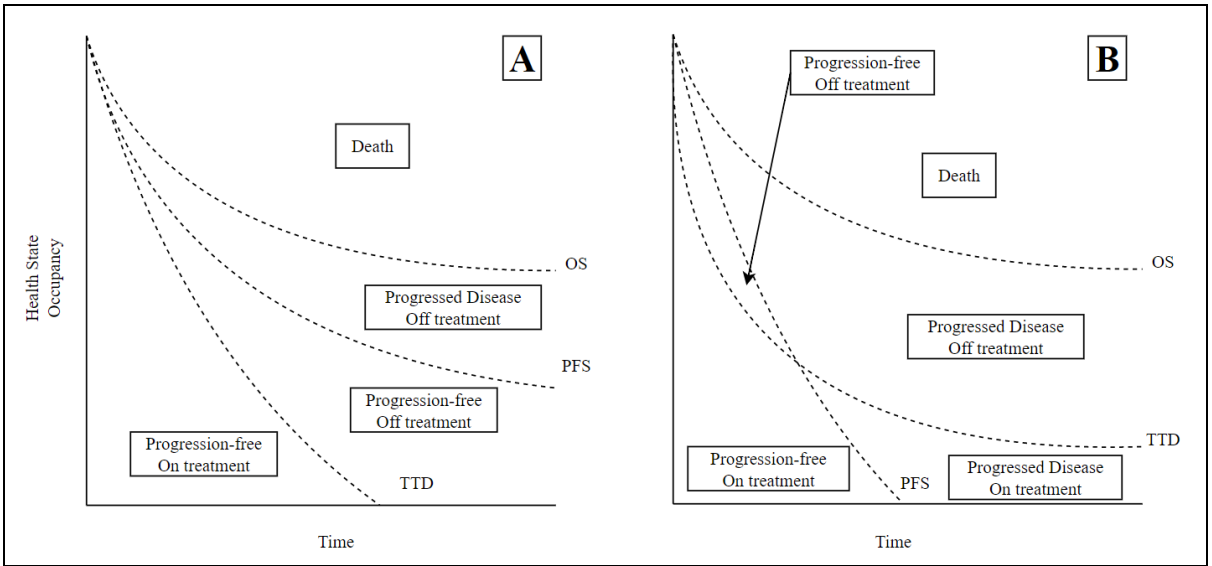


Before generating the overall aggregated results, model results per tumour site were generated to compare outcomes for patients treated with pembrolizumab versus each of the available comparator therapies. In several tumour sites, there are multiple therapies available. Where this is the case, base case results are presented comparing pembrolizumab versus a tumour site-specific weighted SoC. Outcomes for the weighted SoC are derived by weighting individual comparator results by the market share estimates provided by UK clinicians and reflect the variation seen in treatment practices for previously treated MSI-H/dMMR tumours.

The model uses a partitioned survival analysis structure with three mutually exclusive health states: pre-progression, progressed disease (PD) and death. All patients enter the model in the 'progression-free' state and receive treatment with pembrolizumab or a relevant comparator treatment. Patients may remain progression-free, they may progress, or they may die. Patients whose disease has progressed can remain alive with PD or die, with death being the absorbing state. To accurately capture drug administration and acquisition costs, alive states are further separated into on and off treatment.

The de novo partitioned survival analysis uses independently modelled time to treatment discontinuation (TTD), PFS and OS curves to calculate health state occupancy (Section B.3.3.2). The area under the curve approach is used to calculate health state occupancy over time, as shown graphically in Figure 15, with the notes below describing in more detail how modelled patient transitions are calculated. Figure 15A describes the scenario where TTD always remains less than PFS and therefore no patients enter the progressive disease on treatment state. Figure 15B describes the opposite scenario where modelled TTD exceeds PFS and therefore indicates some patients remain on treatment while in the PD state. Whilst the available data indicate patients discontinue treatment at or prior to progression, the model remains flexible to test alternative scenarios (Section B.3.11.3). The figures below are provided for illustrative purposes only and do not reflect the observed data.

Figure 15 Health state occupancy over time



Abbreviations: OS, overall survival; PFS, progression-free survival, TTD, time to treatment discontinuation.
Notes: Figure 15A describes a situation where PFS > TTD. Death = 1-OS, Progressed disease off treatment = OS – PFS, Progression-free off treatment = PFS – TTD, progression-free on treatment = TTD. When PFS > TTD, no patients transition to the progressed disease on treatment state. Figure 15B describes the rare situation where PFS ≤ TTD. Calculations informing patient transitions remain the same except for a few exceptions. Where PFS ≤ TTD: Progression-free on treatment = PFS, progression-free off treatment occupancy is 0, progressed disease on treatment = TTD – PFS, progressed disease off treatment = OS – TTD.

The partitioned survival model structure is both simple and flexible enough to extrapolate survival using various methods and can incorporate relative efficacy in numerous ways. Furthermore, given the model needs to simultaneously consider several indications, complexity must be reduced, where possible, to avoid modelling becoming impractical. Partitioned survival models allow for key trial endpoints such as OS and PFS to be modelled directly, and reflect the clinical pathway of disease in that, once progressed, patients cannot return to the pre-progression state. Progression is a common clinical marker to stop treatment and correlates with patient quality of life. Data for both PFS and OS are readily available from the published evidence for alternative therapies, which is critical to generate comparator survival outcomes given that both KN-164 and KN-158 are single-arm trials. There is also a precedent of using the partitioned survival structure in the modelling of unresectable or metastatic tumours in NICE technology appraisals, including previous appraisals of histology-independent therapies and eight of the nine appraisals identified for the tumour sites of interest (Appendix G).

One of the common limitations of the partitioned survival analysis approach relates to the modelling of the PD state. The modelling approach assumes OS and PFS curves are independent and therefore only implicitly model the transition from the PD state to death. However, as there are minimal subsequent lines of therapy at the modelled stage of the treatment pathway, this is not thought to be a significant limitation. The health states described allow the accurate modelling of disease severity, use of healthcare resources, health-related quality of life and mortality rates.

B.3.2.2.1 General model settings

The model uses a weekly cycle length to predict the proportion of the population who experience a progression or death event. This length was considered appropriate for the evaluation because it enables the model to reflect the timings of drug administrations associated with both pembrolizumab and comparator therapies for all tumour sites. Weekly cycles further capture a realistic minimum time during which the symptoms or responses can change in UK clinical practice.

Given the mean starting age of 56 to 66 years across tumour sites, a 40-year time horizon is used in the base-case to capture all relevant costs and outcomes experienced by the entire cohort, as this equates to a lifetime time horizon in the patient population. The analysis takes the perspective of the NHS and Personal Social Services (PSS) in England in accordance with the NICE reference case. Both costs and QALYs are discounted at 3.5% in line with NICE guidance.

Consistent with the current NICE methods guidance, the primary model output is the incremental net health benefit, although an incremental cost-effectiveness ratio (ICER) expressed as incremental costs per QALY gained is also presented. Additionally, the model provides an overview of other outcomes, such as life years (LYs) gained, and clinically relevant outcomes, such as predicted median OS and PFS.

Table 40 Features of the economic analysis

Current appraisal		
	Chosen values	**Justification**
Time horizon	Lifetime	Long enough to reflect all important differences in costs or outcomes between

Current appraisal		
	Chosen values	**Justification**
		the technologies being compared, in line with the reference case.(66) Survival benefits for patients treated with pembrolizumab are only fully captured if a lifetime horizon is used.
Source of utilities	HRQL data were collected in the KN-158 trial using EQ-5D-3L questionnaires. Literature-based values, derived from Grothey et al. 2013(67), were used to estimate utility values for CRC. Utilities were assumed to be the same across treatment regimens.	EQ-5D data reported directly from patients with utilities based on public preferences is considered the preferred method by NICE.(66) Where EQ-5D-3L data, or other PRO measures, were not available from KN-164, literature-based assumptions were used.
Source of costs	Drug costs were sourced from MIMS) and eMIT. Administration costs, HCRU costs, and adverse event costs were sourced from the NHS references costs, the PSSRU, previous NICE TAs, and relevant literature.	UK sources considered most reflective of costs incurred by NHS England.
Abbreviations: eMIT, electronic market information tool; HCRU, health care resource use; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PRO, patient-reported outcome; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.		

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The intervention in the model is pembrolizumab 200 mg, given intravenously (IV) every 3 weeks for up to 35 cycles or until progression.(38, 41)

In the clinical trials, patients who achieved a complete response and had been treated with at least eight administrations of pembrolizumab could discontinue treatment, which was reflected in the analyses of trial data informing the cost-effectiveness analysis. Patients who had confirmed disease progression but still experienced clinical benefits without any additional increase in tumour burden could

continue pembrolizumab therapy. This was reflected in the economic analysis using the approach described in Section B.3.3.7.

B.3.2.3.2 Comparators

Given the limited treatment options available for MSI-H/dMMR solid tumours (outlined in Section B.1.3.3), and no direct comparators in the same overall indication (as outlined in the SLR and TLR), relevant comparator therapies were identified by following specific treatment guidelines for each tumour site. In each tumour site, relevant comparators included in the cost-effectiveness analysis were determined by UK treatment guidelines and validated by clinical experts.(1) These comparators were used in the clinical SLR (discussed in Section B.2, and Appendix G), to select relevant published evidence to inform the economic model.

Comparators considered in the model, by tumour site, are listed in Table 41. As explained in the decision problem section, no evidence could be identified for FOLFIRI/FOLFOX in small intestine (as expected by clinicians) and so the identified evidence (nab-paclitaxel) was used as a “proxy” chemotherapy.

Table 41 Included comparators by tumour site

Tumour site	Comparator
CRC	TAS-102
	Pooled FOLFIRI/FOLFOX
Endometrial	Chemotherapy (physician’s choice of paclitaxel or doxorubicin)
Gastric	FOLFIRI
	Paclitaxel
Small intestine	Nab-paclitaxel
Cholangiocarcinoma	mFOLFOX
	mFOLFIRI
Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin	

In the base-case analysis, the comparator treatment arms for each tumour site are applied as a basket of treatments that are considered to reflect the SoC. The expected distributions of these treatment options are informed by consensus opinion on market shares, which was elicited from clinical experts during an advisory board(1), and varied probabilistically to consider the impact of uncertainty. This is described in further detail in Section B.3.5.1.1.2.

B.3.3 Clinical parameters and variables

B.3.3.1 Baseline patient characteristics

Baseline patient characteristics were informed by patients recruited to the KN-158 and KN-164 trials and were dependent on tumour site. Mean age and gender distribution were used to adjust general population mortality data sourced from the Office for National Statistics (ONS).(68) Mean body surface area was calculated using height and weight data using the Mostellar formula.(69) Weight and body surface area were used to calculate accurate dosing for relevant comparator treatments without fixed dose regimens. Population inputs are summarized in Table 42. Further details of patient characteristics from KN-158 and KN-164 are described in Section B.2.3.1.

Table 42 Summary of population inputs

Population	Mean	N (n)	SD	SE	Source
Age					
CRC	56.08	124	14.90	0.031	KN164
Endometrial	64.28	83	8.70	0.036	KN158
Gastric	66.18	51	11.90	0.068	KN158
Small intestine	57.60	27	13.10	0.134	KN158
Cholangiocarcinoma	59.73	22	9.90	0.143	KN158
Patient weight					
CRC	70.00	124	22.00	0.038	KN164
Endometrial	72.50	83	17.50	0.050	KN158
Gastric	61.80	51	15.60	0.077	KN158
Small intestine	71.10	27	15.80	0.147	KN158
Cholangiocarcinoma	67.60	22	15.70	0.180	KN158
Gender (Proportion male)					
CRC	55.65%	124 (69)	-	-	KN164
Endometrial	0.00%	83 (0)	-	-	KN158
Gastric	64.71%	51 (33)	-	-	KN158
Small intestine	62.96%	27 (17)	-	-	KN158
Cholangiocarcinoma	59.09%	22 (13)	-	-	KN158
BSA					
CRC	1.8	124	0.30	0.004	KN164
Endometrial	1.8	83	0.20	0.005	KN158
Gastric	1.7	51	0.20	0.009	KN158
Small intestine	1.8	27	0.20	0.017	KN158
Cholangiocarcinoma	1.8	22	0.20	0.020	KN158

Abbreviations: BSA, body surface area; CRC, colorectal cancer; SD, standard deviation; SE, standard error.

B.3.3.2 Tumour site distribution

To accurately estimate the cost-effectiveness in the overall indication, and therefore the resulting single ICER, it is necessary to aggregate the individual tumour site results. This requires an estimation of the distribution of patients across each constituent tumour site. Two options are available for incorporating tumour site distribution inputs within the model. The first option is to use the number of patients included within each tumour site of the KN-158 and KN-164 trials to inform the distribution. The second is to consider the data observed within current UK clinical practice. These estimates are presented in Table 43.

Trial-based estimates are used in the base case, given the difficulty to accurately estimate real-world distributions across tumour sites.(1) Values were probabilistically sampled to incorporate uncertainty. Tumour site distributions derived from UK epidemiological data in combination with published sources were explored in scenario analyses. Full details of the epidemiological data informing these estimates can be found in the accompanying budget impact analysis element of this submission. To summarize the epidemiological data used, UK sources of cancer incidence for each of the tumour sites were identified from the published literature. These estimates were then adjusted to account for the proportion of patients at diagnosis with different disease stages as well as the proportion of patients expected to progress through the treatment pathway and remain eligible for further active therapy. The resulting calculations allowed the total eligible population in each tumour site to be calculated, which was then used to calculate the tumour site distribution based on published data.

Table 43 Tumour site distribution model inputs

Tumour site	Distribution	
	Trial based	UK epidemiological data
CRC	40.39%	31.44%
Endometrial	27.04%	24.03%
Gastric	16.61%	31.19%
Small intestine	8.79%	8.60%
Cholangiocarcinoma	7.17%	4.75%

Abbreviations: CRC, colorectal cancer.
Source: Trial based; KN-158 and KN-164.(70, 71) UK epidemiological data, see budget impact submission.

B.3.3.3 Time-to-event analysis overview

OS, PFS and TTD were used to inform health state occupancy in the economic analysis. For pembrolizumab, data collected from the single-arm KN-164 and KN-158 trials were used to inform the time-to-event outcomes. In the absence of a direct treatment comparison in these trials, indirect treatment comparisons were required to compare pembrolizumab to clinically relevant comparators within each tumour site.

B.3.3.3.1 Pembrolizumab

Analyses of pembrolizumab survival outcomes were conducted using theASaT population, which consists of all allocated participants who have received at least one dose of study treatment. Data correspond to the 19 February 2021 cutoff date for KN-164 and the 15 October 2021 cutoff date for KN-158. A later data-cut is available for KN-158 (12 January 2022), however, as explained previously, the additional 3 months of follow-up result in very few additional OS and PFS events and is therefore unlikely to make a meaningful difference to cost-effectiveness analysis results (see B.2.6.3).

Heterogeneity is a key theme in analysing data that are collected for patients treated with therapies used across multiple tumour sites – and a theme that specifically arises when data are collected as part of a basket trial, such as KN-158. Various assumptions may be made about heterogeneity, or the lack thereof, in outcomes between the different tumour types that are represented. To ensure heterogeneity was carefully considered and explored when modelling patient survival, various approaches were used to model OS and PFS for pembrolizumab, and can be summarized into the following:

- Bayesian hierarchical models (BHMs)
- Standard parametric modelling independent to tumour sites

Detail around the methodology and assumptions behind the BHM and standard parametric modelling approaches is provided in Sections B.3.3.3.1.1 and B.3.3.3.2.1, respectively. An alternative approach to BHM and independent parametric modelling would be to assume that there is complete homogeneity in survival outcomes across tumour sites; in essence, survival outcomes in different tumour sites are equal, or

differences in survival outcomes between tumour sites are negligible. Under this assumption, data from different tumour sites can be pooled and analysed together. However, based on the exploration of heterogeneity of survival outcomes conducted as part of the BHM analysis, as well as feedback provided by UK clinical experts, an analysis assuming complete homogeneity by pooling data across multiple tumour sites was considered implausible and therefore not considered further.(1)

TTD data collected from KN-164 and KN-158 were mature and did not require extrapolation as the Kaplan–Meier function could be incorporated directly into modelling.

B.3.3.3.1.1 Bayesian hierarchical modelling

The updated NICE methods guide recommends the use of BHMs as a suitable statistical method to explore and capture heterogeneity. These methods represent a middle ground between the strong assumptions of total tumour site independence (each tumour site within KN-158 is a separate trial dataset) and complete homogeneity (pooling all tumour site data within KN-158). BHMs assume that outcomes, or the efficacy of the intervention, is similar across different tumour sites, and the different tumour sites do not determine a particular ordering of effectiveness a priori (i.e. the tumour sites are exchangeable).

However, BHMs represent a relatively novel statistical method that up until now, no published studies or NICE appraisals have used to analyse time-to-event outcomes. Previous similar economic evaluations submitted to NICE have simplistically assumed complete homogeneity of outcomes between tumour sites despite the presence of heterogeneity.(72, 73) A report by researchers at the University of York and University of Sheffield suggested that Bayesian hierarchical methods ‘may provide a useful vehicle with which to explore any heterogeneity’.(74) Similarly, in both the appraisals of entrectinib and larotrectinib for treating *NTRK* fusion-positive solid tumours, the External Assessment Group (EAG) applied BHM models to dichotomous response outcomes and used these to weight parametric survival extrapolations. However, the EAG could not apply the BHM to time-to-event outcomes given the data provided by the company but did recommend that heterogeneity in time-to-event outcomes should be explored using a BHM in future

appraisals and that this approach should “assume a common parametric distribution across each tumour site but with a different location parameter”.(73) It is this novel approach that has been used to extrapolate pembrolizumab OS and PFS survival outcomes in the current evaluation. BHMs capture heterogeneity between tumour sites and allow information to be borrowed between groups or ‘baskets’ through the use of shared parameters. This method aims to increase the precision of estimates when compared to analysing individual baskets separately, while also reducing the chances of obtaining implausible estimates for tumour sites represented by few patients.(75, 76)

The hierarchical nature means that parametric distributions fitted using this approach have both shared (fixed-effects) parameters and tumour-site-dependent parameters. Fixed-effects parameters are shared by all tumour sites while an exchangeable (random-effects) parameter that is unique to each tumour site captures the heterogeneity of outcomes observed. The location (or scale/rate parameter) is a function of these fixed effects, as well as the random effects which is consistent with the model described by the external assessment group (EAG) above. The following parametric distributions were explored using this approach: exponential, Weibull, Gompertz, log-normal and log-logistic.

Covariates were selected for inclusion within the BHM based on clinical expert opinion and an exploratory analysis of the available data. The fixed-effects covariates used to adjust extrapolated pembrolizumab survival were:

- Age
- Gender
- ECOG score
- Cancer stage
- Number of prior lines of therapy

As an extension to the one-piece BHM approach, a piecewise BHM was also explored for PFS outcomes only to account for the poor fit of the one-piece

distributions to the observed Kaplan–Meier function between 0 and 10 weeks. This was due to a sharp drop in PFS since the first on-study imaging time point was performed at 9 weeks in both KN-164 and KN-158.(70, 71)

B.3.3.3.1.2 Standard parametric modelling

To further explore the impact of heterogeneity, a supporting scenario was explored whereby tumour sites were considered independently with standard parametric distributions fitted separately to survival data from KN-164 and KN-158 for each tumour site (i.e. equivalent to treating each tumour site as a standalone trial). The term 'standard' refers to the use of a set of one-piece distributions fitted in a frequentist framework, as opposed to using Bayesian methods, which have been described above. The term 'one-piece' is used to describe where a single model is fitted to the entire follow-up period. This approach effectively assumes independence between tumour sites and does not allow borrowing of OS/PFS data from different tumour sites; the uncertainty for any given tumour is therefore expected to be substantially higher than under the BHM approach.

B.3.3.3.2 Standard of care

Analyses of comparator survival outcomes were informed by published studies identified by the clinical SLR. A summary of the published studies informing each comparison are provided in Section B.2.8. All comparators except for paclitaxel in the gastric tumour site and TPC (paclitaxel/doxorubicin) in the endometrial tumour site were informed by studies of patients unselected for MSI-H/dMMR status. Despite evidence suggesting MSI-H/dMMR status is prognostic of worse survival outcomes, no adjustment was made in the economic model, this is considered to be a conservative assumption.(22) Various methods to derive comparative efficacy were explored in the model; these can be summarized into the following:

- Hazard ratios derived from unadjusted ITCs
- Hazard ratios derived from MAIC
- Independent fitted parametric curves to comparator KM curves
- Non-responder analysis

As described in Section B.2.8, given **1**) the proportional hazards assumption was violated in all cases, **2**) the impact of population adjustment for observed confounders (via MAIC) was negligible and **3**) flexible methods to derive time-varying HRs were not feasible, comparator survival outcomes were modelled using independently-fitted parametric survival distributions. Note, that for transparency, the economic model includes functionality to apply these estimates of relative effectiveness to clearly demonstrate that corresponding survival outcomes are implausible. Further detailed results, log-cumulative hazard and Schoenfeld residual plots, and extrapolations are provided in Appendix P (unadjusted ITCs) and Appendix Q (MAIC).

Detail around the methodology and assumptions behind the standard parametric modelling and non-responder analysis approaches is provided in Section B.3.3.3.2.1.

Comparator TTD data were not publicly available for the selected comparators. Consequently, the model assumed TTD was equivalent to PFS (where this assumption was supported by clinical experts), or an exponential distribution was fitted to median TTD where possible. These approaches ensured the best use of the available data.

B.3.3.3.2.1 Standard parametric modelling

The same standard parametric modelling methods, as described above in Section B.3.3.3.1.2, were used to extrapolate survival outcomes for the comparator arms. OS and PFS KM data, where available from the SLR, were used. This allowed parametric survival distributions to be fitted to the digitized data.

B.3.3.3.2.2 Pembrolizumab non-responder analysis

In the absence of randomized controlled trial data, previous studies have suggested use of surrogacy assumptions to inform estimates of relative efficacy.(74, 77) A proposed approach is to use a non-responder analysis. The basic assumption of this method is patients treated with pembrolizumab from KN-158 and KN-164 who do not achieve a partial or complete response are assumed to have survival outcomes that are consistent with patients who received a comparator treatment within established

clinical practice. This analysis was done separately for each tumour site using standard parametric models fitted to data collected from non-responders.

A limitation of this analysis is that there is little evidence to suggest that non-responders are a suitable surrogate for comparator OS and PFS outcomes in this indication. Furthermore, due to the small patient numbers and exacerbated by the high level of disease response demonstrated by pembrolizumab, there were few non-responder patients to collect data from for this approach. For these reasons, this approach was not formally considered in the economic analysis.

B.3.3.3.3 Summary of approaches explored

Table 44 and Table 45 summarize the key assumptions and methods used for modelling pembrolizumab and comparator efficacy. Table 44 outlines the key assumptions that are needed for each method, denoted by the tick marks. Table 45 gives further details on these assumptions in relation to the cost-effectiveness model. For these tables, the Bayesian hierarchical modelling rows refer to both standard and piecewise BHM approaches.

Table 44 Summary grid of methods explored to derive pembrolizumab and comparator efficacy

Methods for extrapolating pembrolizumab OS and PFS	Methods for producing comparator OS and PFS	Key assumptions behind approach				
		Complete heterogeneity in (absolute) pembrolizumab efficacy across tumour sites	Significant (absolute) pembrolizumab efficacy modifiers	Significant relative efficacy modifiers	Proportional hazards assumption holds	Pembrolizumab non-responders are a proxy for comparator treatments
Bayesian hierarchical models	MAIC	✘	✓	✓	✓	✘
	Unadjusted ITC	✘	✓	✘	✓	✘
	Independently fitted parametric curves to comparator KMs	✘	✓	✘	✘	✘
	Non-responder analysis	✘	✓	✘	✘	✓
Standard parametric models	MAIC	✓	✘	✓	✓	✘
	Unadjusted ITC	✓	✘	✘	✓	✘
	Independently fitted parametric curves to comparator KMs	✓	✘	✘	✘	✘
	Non-responder analysis	✓	✘	✘	✘	✓

Abbreviations: ITC, indirect treatment comparison; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

Table 45 Summary of methods explored to derive pembrolizumab and comparator efficacy

Methods for extrapolating pembrolizumab OS and PFS	Methods for producing comparator OS and PFS			
	MAIC	**Unadjusted ITC**	**Independently fitted parametric curves to comparator KMs**	**Non-responder analysis**
Bayesian hierarchical models	• Pembrolizumab efficacy allows for heterogeneity between tumour sites and controls for various potential (absolute) efficacy modifiers • Relative efficacy (vs comparator) is adjusted for potential treatment effect modifiers • Assumes proportional hazards holds	• Pembrolizumab efficacy allows for heterogeneity between tumour sites and controls for various potential (absolute) efficacy modifiers • Assumes there are no significant relative efficacy (vs comparator) modifiers • Assumes proportional hazards holds	• Pembrolizumab efficacy allows for heterogeneity between tumour sites and controls for various potential (absolute) efficacy modifiers • Assumes there are no significant relative efficacy (vs comparator) modifiers	• Pembrolizumab efficacy allows for heterogeneity between tumour sites and controls for various potential (absolute) efficacy modifiers • It can be assumed that comparator efficacy is broadly similar to patients who do not respond to pembrolizumab
Standard parametric models fitted by tumour site	• Pembrolizumab efficacy is assumed to be independent by tumour site (i.e. perfect heterogeneity across sites) and there are no other efficacy modifiers • Relative efficacy (vs comparator) is adjusted for potential treatment effect modifiers • Assumes proportional hazards hold	• Pembrolizumab efficacy is assumed to be independent by tumour site (i.e. perfect heterogeneity across sites) and there are no other efficacy modifiers • Assumes there are no significant relative efficacy (vs comparator) modifiers • Assumes proportional hazards holds	• Pembrolizumab efficacy is assumed to be independent by tumour site (i.e. perfect heterogeneity across sites) and there are no other efficacy modifiers • Assumes there are no significant relative efficacy (vs comparator) modifiers	• Pembrolizumab efficacy is assumed to be independent by tumour site (i.e. perfect heterogeneity across sites) and there are no other efficacy modifiers • It can be assumed that comparator efficacy is broadly similar to patients who do not respond to pembrolizumab

Abbreviations: ITC, indirect treatment comparison; KM, Kaplan–Meier; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival.

B.3.3.4 Selection of methods in the base case

KN-158 and KN-164 data extrapolated over a lifetime horizon are used to inform health state occupancy in the model using an area-under-the-curve approach. The approaches explored for pembrolizumab and the comparator treatments are outlined in the above sections.

In accordance with the NICE DSU TSD 14 guidance on survival analyses(78), a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalized gamma) were explored for the extrapolation of OS and PFS KM data. Generalized gamma could not be explored for BHM because the model consistently failed to converge.

The suitability of each method described was assessed using the following criteria:

- Visual inspection to assess the fit of the model to the KM curve
- Goodness-of-fit criteria including the Akaike information criterion (AIC), the Bayesian information criteria (BIC) and, where relevant, the deviance information criterion (DIC)
- Validation against published long-term survival data
- Clinical plausibility for both short- and long-term estimates of survival, based on clinical expert validation

In addition, although formal mixture cure modelling is not considered, distributions selected to extrapolate pembrolizumab survival outcomes are consistent with the clinical consensus that there is a ‘functionally cured’ proportion of patients across tumour sites that would be expected due to the immunomodulatory effects of pembrolizumab. Clinical opinion suggested that this group of patients is established at around 5 years after treatment initiation and that it would be expected that their probability of death after this point is broadly consistent with that of an age-adjusted general population mortality.(1) The clinical feedback regarding functional cure was corroborated by assessment of the observed hazard function for pembrolizumab in each tumour site, showing the hazard steadily declining to a negligible value at the

end of the follow-up period. It should be noted that no explicit cure assumption is implemented (e.g. risks of death/progression restricted at 5 years or alternative survival models) but should be considered in curve selection and assessment of plausibility of extrapolations.

Given that the BHMs were fitted across all tumour sites, suitability was also assessed across all tumour sites simultaneously, taking into consideration overall fit, clinical plausibility, and the relative size of the populations for each tumour site. This may result in the visual fits of some tumour sites, particularly those with small individual sample sizes, appearing worse than when fitted independently; however, it should be considered that this results from the models being fitted to more than just the individual tumour site data due to "borrowing" from the other tumours.

B.3.3.5 Overall survival

B.3.3.5.1 Pembrolizumab

For the CRC tumour site, informed by KN-164, OS is defined as the time from the date of the first dose to death due to any cause, expressed in weeks. For the tumour sites informed by KN-158, OS is defined as the time from allocation to death due to any cause, expressed in weeks. Patients without documented death are considered right censored at the date of last contact. Participants who had survival updates after the data cutoff date in their specific protocol are censored at that cutoff date.

The OS KM data for patients treated with pembrolizumab in KN-164 and KN-158 are presented in Figure 16.

Figure 16 Pembrolizumab (KN-164, KN-158) – OS

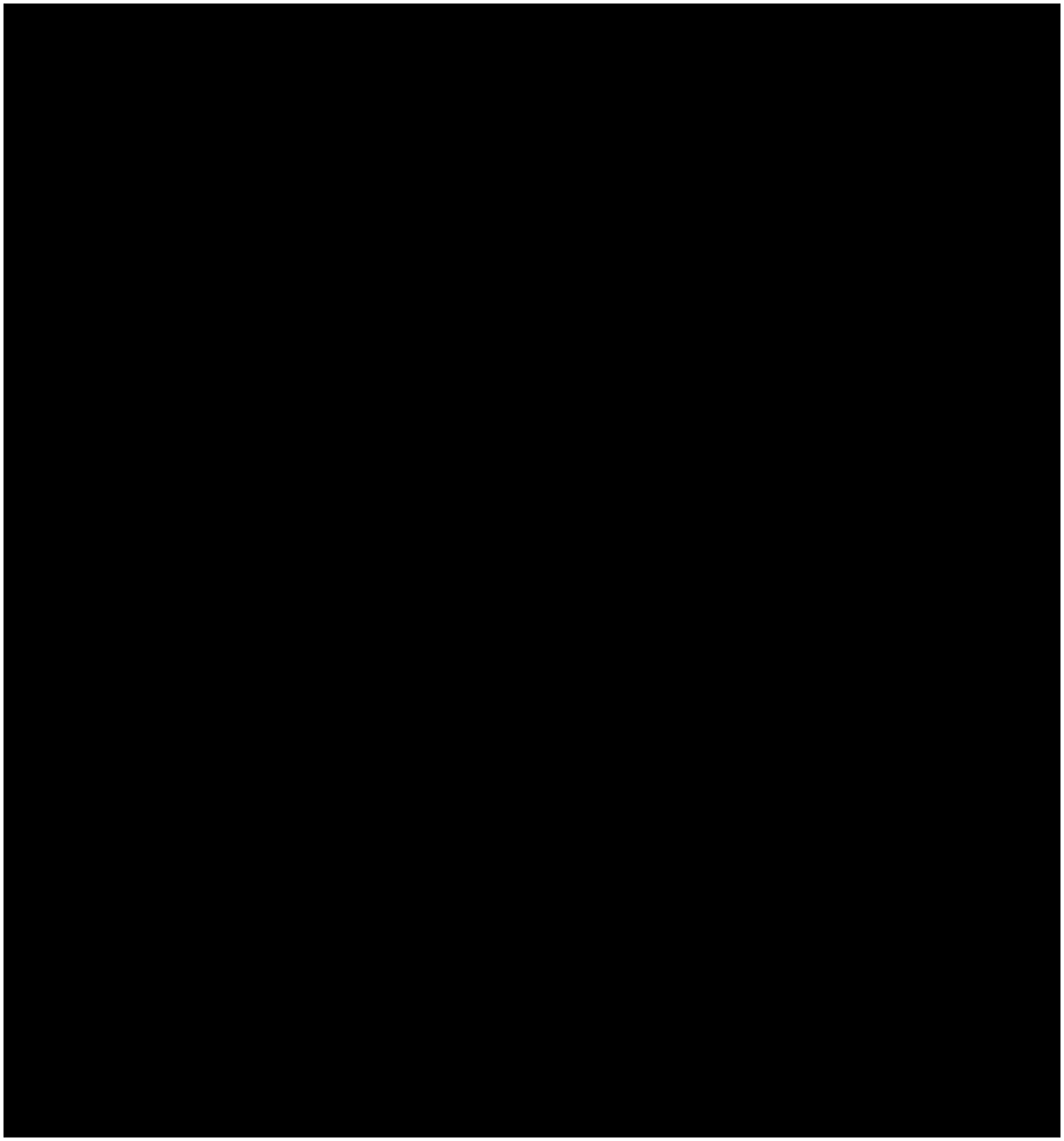
Bayesian hierarchical modelling was selected for the base case to model pembrolizumab OS and to capture heterogeneity between tumour sites, as discussed in Section B.3.3.3.1.

Figure 17 shows the pembrolizumab extrapolation beyond the observed follow-up period of the trial. Table 46 gives the DIC for the BHM curves for pembrolizumab. Among all considered parametric models, the log-normal and log-logistic models have the lowest DIC, which indicates that they fit the observe data well. These are followed by the Weibull model, which has the third best statistical fit. The exponential and Gompertz models have the highest DIC, which indicates that they fit the observed data poorly.

During the UK advisory board, clinical expert opinion highlighted that the log-normal, log-logistic and Weibull resulted in plausible survival projections, and that the exponential and Gompertz were overly pessimistic as they do not capture the favourable outcomes expected in the functionally cured population.(1)

For the base case, the log-normal model was selected based on statistical fit, comparison of the observed versus the predicted hazard functions, clinical expert opinion, and visual fit to the Kaplan–Meier data. The base case OS extrapolations also included treatment waning as described in Section B.3.3.9. Figure 17 presented below shows pembrolizumab OS extrapolations unadjusted for treatment waning. The Weibull model, as well as analyses assuming no treatment effect waning, were explored in scenario analyses.

Figure 17 BHM – Pembrolizumab OS



Abbreviations: BHM, Bayesian hierarchical modelling; CRC, colorectal cancer; KM, Kaplan–Meier; OS, overall survival.

Table 46 BHMs statistical fit – OS

Parametric model	DIC
Exponential	[redacted]
Weibull	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]

Abbreviations: BHM, Bayesian hierarchical model; DIC, deviance information criterion; OS, overall survival.

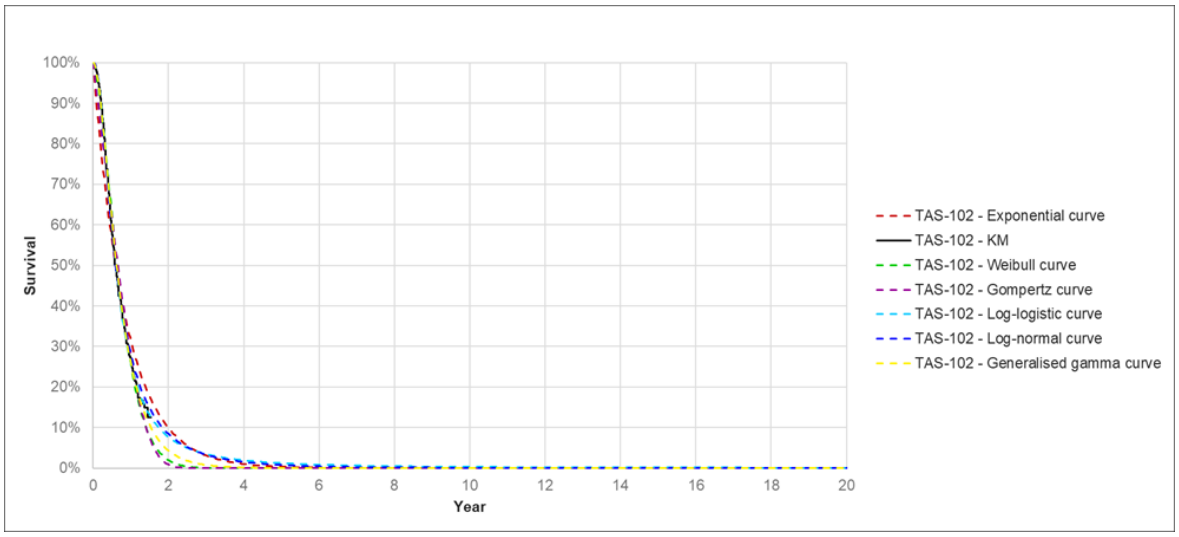
B.3.3.5.2 Comparators

For comparator treatments, individual fitted curves for each tumour site were chosen for the base case. Selected comparator extrapolations beyond the observed follow-up period of the trial are given in Figure 18, Figure 19, Figure 20, Figure 21 and Figure 22 for each tumour site. Respective AIC/BIC values are given in Table 47, Table 48, Table 49, Table 50 and Table 51.

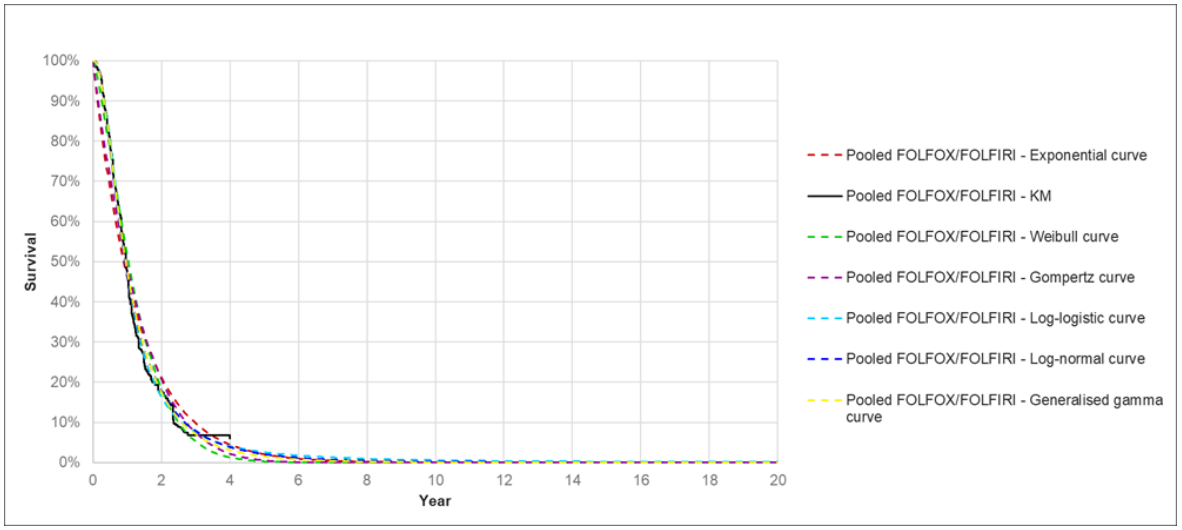
Table 52 summarizes the best fitting curves for each comparator for each tumour site. The parametric distribution selected in the base case for each tumour site was primarily based on visual and statistical fit, given that the data were mature. UK clinical experts validated the selected curves and confirmed that extrapolations were clinically plausible.

Figure 18 Standard parametric modelling – CRC – OS

TAS-102



Pooled FOLFOX/FOLFIRI



Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; KM, Kaplan–Meier; OS, overall survival.

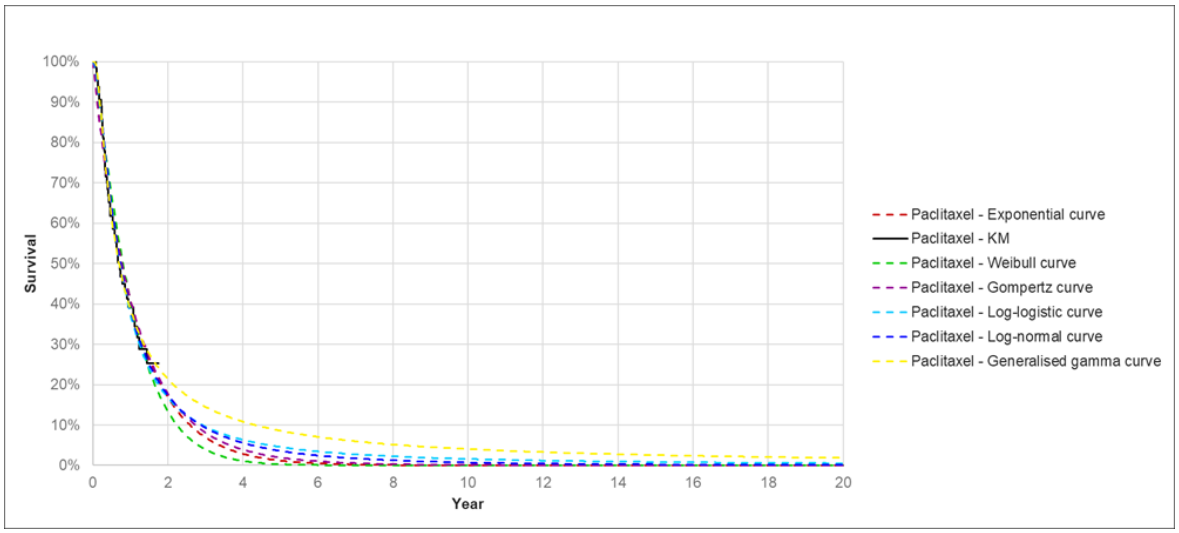
Table 47 Best fitting curves – CRC – OS

Parametric model	TAS-102		Pooled FOLFOX/FOLFIRI	
	AIC	BIC	AIC	BIC
Exponential	3493.82	3498.10	6302.91	6307.43
Weibull	3414.42	3422.98	6221.58	6230.61
Gompertz	3455.74	3464.30	6292.20	6301.24
Log-logistic	**3397.65**	**3406.21**	**6136.93**	**6145.97**
Log-normal	3417.29	3425.85	6158.24	6167.27
Generalized gamma	3404.45	3417.30	6156.98	6170.54

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CRC, colorectal cancer; OS, overall survival.

Figure 19 Standard parametric modelling – Endometrial cancer – OS

Paclitaxel or doxorubicin



Abbreviations: KM, Kaplan–Meier; OS, overall survival.

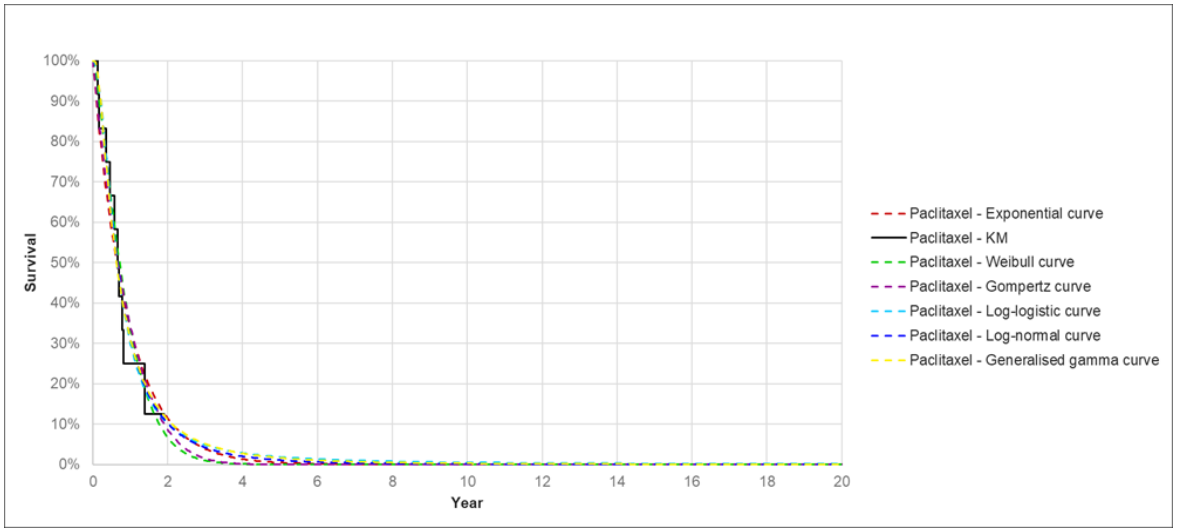
Table 48 Best fitting curves – Endometrial cancer – OS

Parametric model	Paclitaxel or doxorubicin	
	AIC	BIC
Exponential	428.00	430.18
Weibull	428.67	433.02
Gompertz	429.97	434.32
Log-logistic	423.94	428.29
Log-normal	**422.17**	**426.52**
Generalized gamma	422.68	429.20

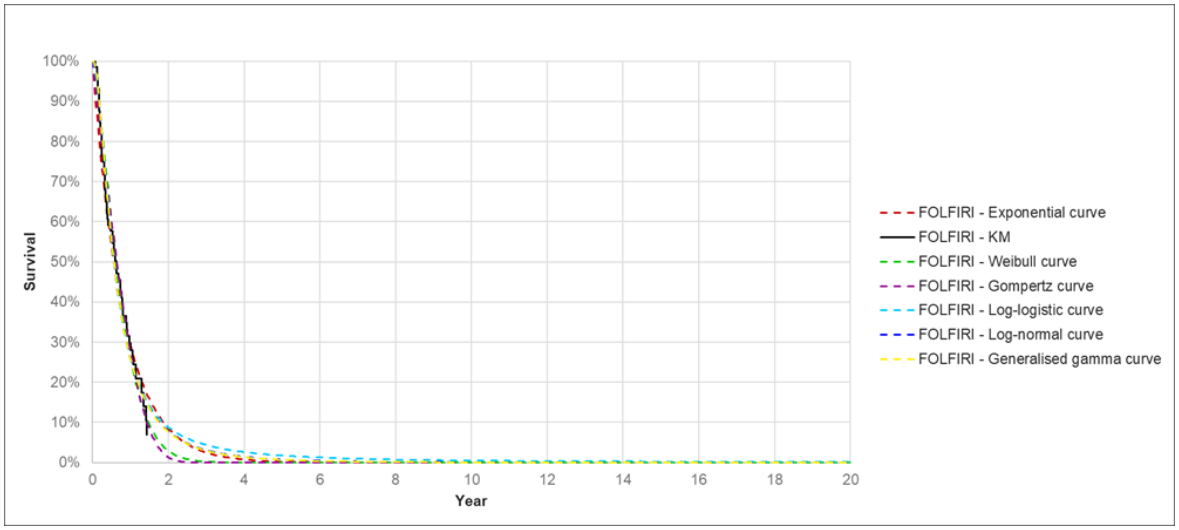
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.
Notes: Efficacy inputs for paclitaxel and doxorubicin are the same for both treatments in the cost-effectiveness model.

Figure 20 Standard parametric modelling – Gastric cancer – OS

Paclitaxel



FOLFIRI



Abbreviations: FOLFIRI, folinic acid, fluorouracil and irinotecan; KM, Kaplan–Meier; OS, overall survival.

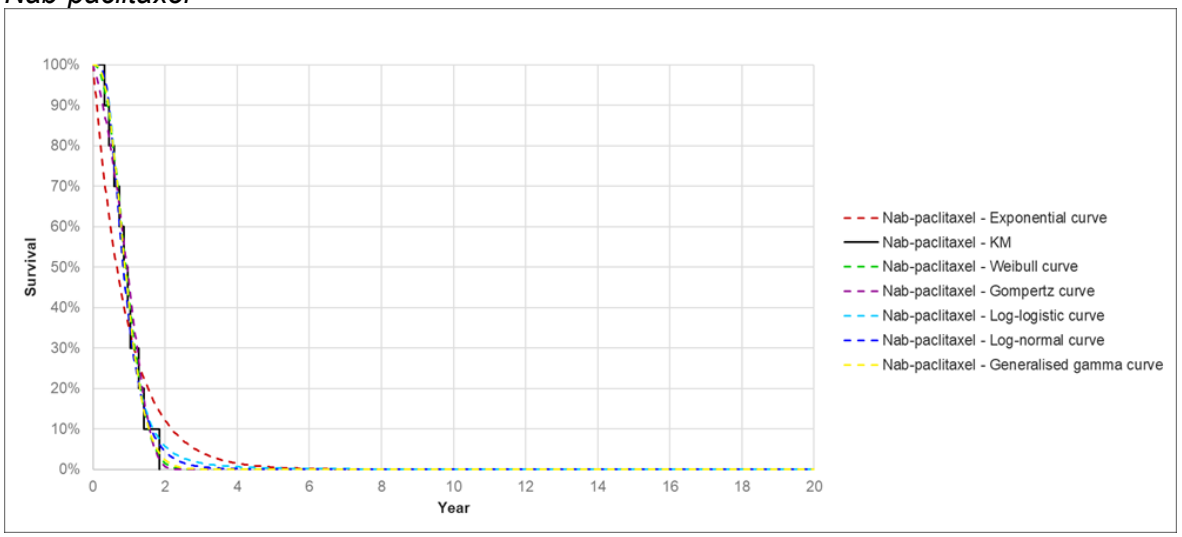
Table 49 Best fitting curves – Gastric cancer – OS

Parametric model	Paclitaxel		FOLFIRI	
	AIC	BIC	AIC	BIC
Exponential	99.50	**99.99**	533.53	535.85
Weibull	100.46	101.43	527.28	531.92
Gompertz	101.36	102.33	530.28	534.91
Log-logistic	99.33	100.30	527.37	532.01
Log-normal	**99.29**	100.26	**524.43**	**529.07**
Generalized gamma	101.26	102.72	526.43	533.38

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, folinic acid, fluorouracil and irinotecan; OS, overall survival.

Figure 21 Standard parametric modelling – Small intestinal cancer – OS

Nab-paclitaxel



Abbreviations: KM, Kaplan–Meier; OS, overall survival.

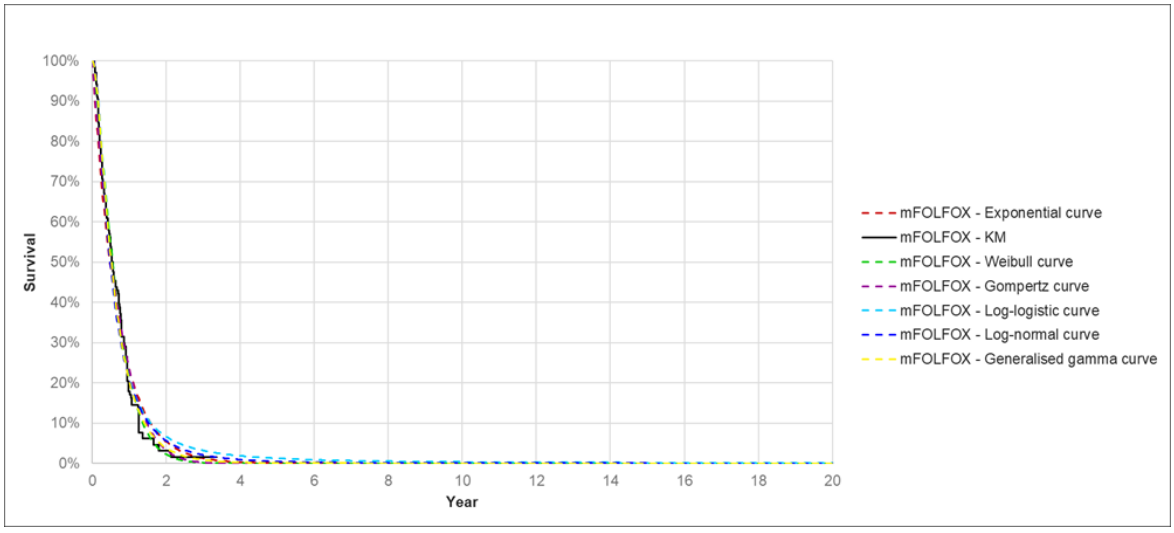
Table 50 Best fitting curves – Small intestine cancer – OS

Parametric model	Nab-paclitaxel	
	AIC	BIC
Exponential	100.00	100.31
Weibull	**94.24**	**94.84**
Gompertz	95.45	96.06
Log-logistic	95.08	95.68
Log-normal	94.51	95.11
Generalized gamma	96.13	97.04

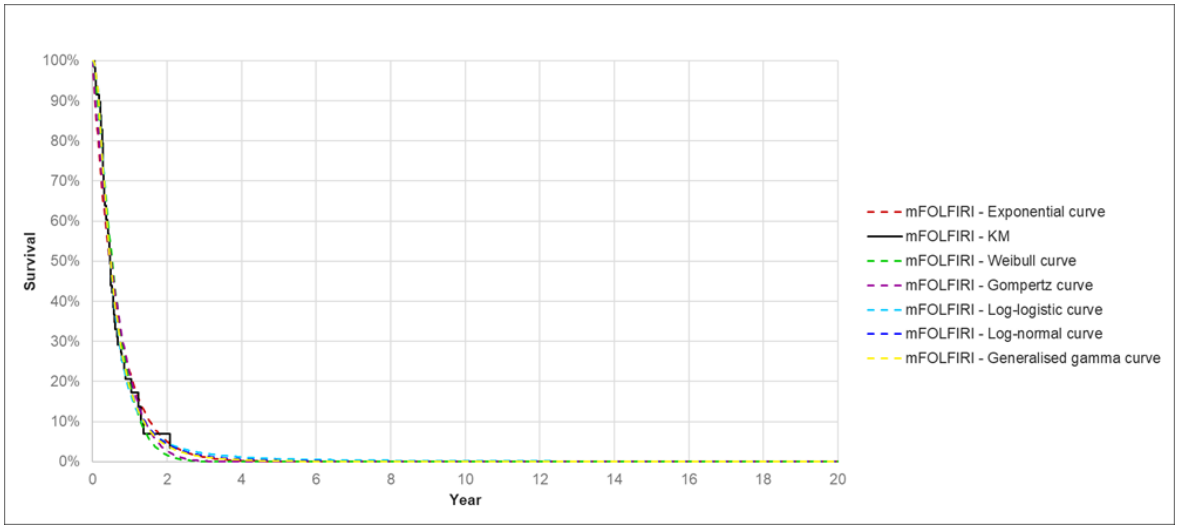
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Figure 22 Standard parametric modelling – Cholangiocarcinoma – OS

mFOLFOX



mFOLFIRI



Abbreviations: mFOLFIRI, modified folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; KM, Kaplan–Meier; OS, overall survival.

Table 51 Best fitting curves – Cholangiocarcinoma – OS

Parametric model	mFOLFOX		mFOLFIRI	
	AIC	BIC	AIC	BIC
Exponential	1118.53	1121.45	448.18	450.26
Weibull	1107.27	1113.11	444.07	448.22
Gompertz	1117.20	1123.04	449.15	453.31
Log-logistic	1108.38	1114.22	**438.18**	**442.34**
Log-normal	1104.79	**1110.63**	438.59	442.74
Generalized gamma	**1104.40**	1113.16	440.53	446.76

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFIRI, modified folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; OS, overall survival.

Table 52 Summary of best fitting curves from ITC – OS

Comparator	AIC	BIC	Base case
CRC			
TAS-102	Log-logistic	Log-logistic	Log-logistic
Pooled FOLFOX/FOLFIRI	Log-logistic	Log-logistic	Log-logistic
Endometrial			
Paclitaxel or doxorubicin	Log-normal	Log-normal	Log-normal
Gastric			
Paclitaxel	Log-normal	Exponential	Gompertz
FOLFIRI	Log-normal	Log-normal	Weibull
Small intestine			
Nab-paclitaxel	Weibull	Weibull	Weibull

Comparator	AIC	BIC	Base case
Cholangiocarcinoma			
mFOLFOX	Generalized gamma	Log-normal	Log-normal
mFOLFIRI	Log-logistic	Log-logistic	Log-normal

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CRC, colorectal cancer; (m)FOLFIRI, (modified) folinic acid, fluorouracil and irinotecan; mFOLFOX, (modified) folinic acid, fluorouracil and oxaliplatin; ITC, indirect treatment comparison; OS, overall survival.
Note: The best statistical fit was used to inform base case selections, except where curves resulted in an implausibly long tail for comparator therapies. In these instances, visual fit and clinical plausibility took precedence.

B.3.3.5.3 Summary of OS base case

The below figures show the selected base case curves for both pembrolizumab and comparators for each tumour site of interest. The selection criteria for the modelling methods and the parametric curves are given in Section B.3.3.4. Results are insensitive to alternative comparator OS selections and show a sustained OS benefit for pembrolizumab compared with chemotherapy for each tumour site (consistent with clinical expectations), which is reflected in the cost-effectiveness results.

Figure 23 Selected base case curve – CRC – OS

Figure 24 Selected base case curve – Endometrial – OS

Figure 25 Selected base case curve – Gastric – OS

Figure 26 Selected base case curve – Small intestine – OS

Figure 27 Selected base case curve – Cholangiocarcinoma – OS

Abbreviations: CRC, colorectal cancer; (m)FOLFIRI, (modified) folinic acid, fluorouracil and irinotecan; (m)FOLFOX, (modified) folinic acid, fluorouracil and oxaliplatin; KM, Kaplan–Meier; OS, overall survival.

B.3.3.6 Progression-free survival

B.3.3.6.1 Pembrolizumab

As described in Section B.2.3, PFS is defined as the time from randomization to the date of the first documentation of disease progression, according to RECIST 1.1. PFS was assessed by independent review committee, or death due to any cause (whichever occurs first).

The survival outcomes for patients treated with pembrolizumab in KN-164 and KN-158 are presented in Figure 28 for PFS.

Figure 28 Pembrolizumab (KN-164, KN-158) – PFS

BHM was selected for the base case to model pembrolizumab PFS to allow for heterogeneity between tumour sites, consistent with the methods described and used for OS.

Figure 29 shows the pembrolizumab extrapolation beyond the observed follow-up period of the trial and predicted survival. Table 53 gives the DIC for the BHM curves for pembrolizumab. Among all considered parametric models, the log-normal, log-logistic and Weibull models have the lowest DIC (indicating a good model fit among those models), while the exponential and Gompertz models have the highest DIC (indicating a worse fit among the considered models).

Clinical expert opinion highlighted that the log-normal, log-logistic and Weibull were plausible curves, with the exponential and Gompertz being implausible and too pessimistic as they do not capture the functionally cured population.(1) For the base case, the log-normal was selected based on statistical fit, clinical expert opinion, and visual fit to the Kaplan–Meier data.

As introduced in Section B.3.3.3.1.1, an exploratory analysis using a piecewise BHM model was fitted to extrapolate pembrolizumab PFS outcomes from 10 weeks onwards, given the poor fit of ‘one-piece’ distributions to the observed Kaplan–Meier function between 0 and 10 weeks. This analysis was conducted in line with NICE DSU TSD 21 and was investigated in scenario analyses.(79) Flexible methods for survival analysis, such as piecewise methods, were not feasible for the separate analysis of individual tumour sites given the limited patient numbers available in each tumour site.

Figure 29 BHM – Pembrolizumab PFS

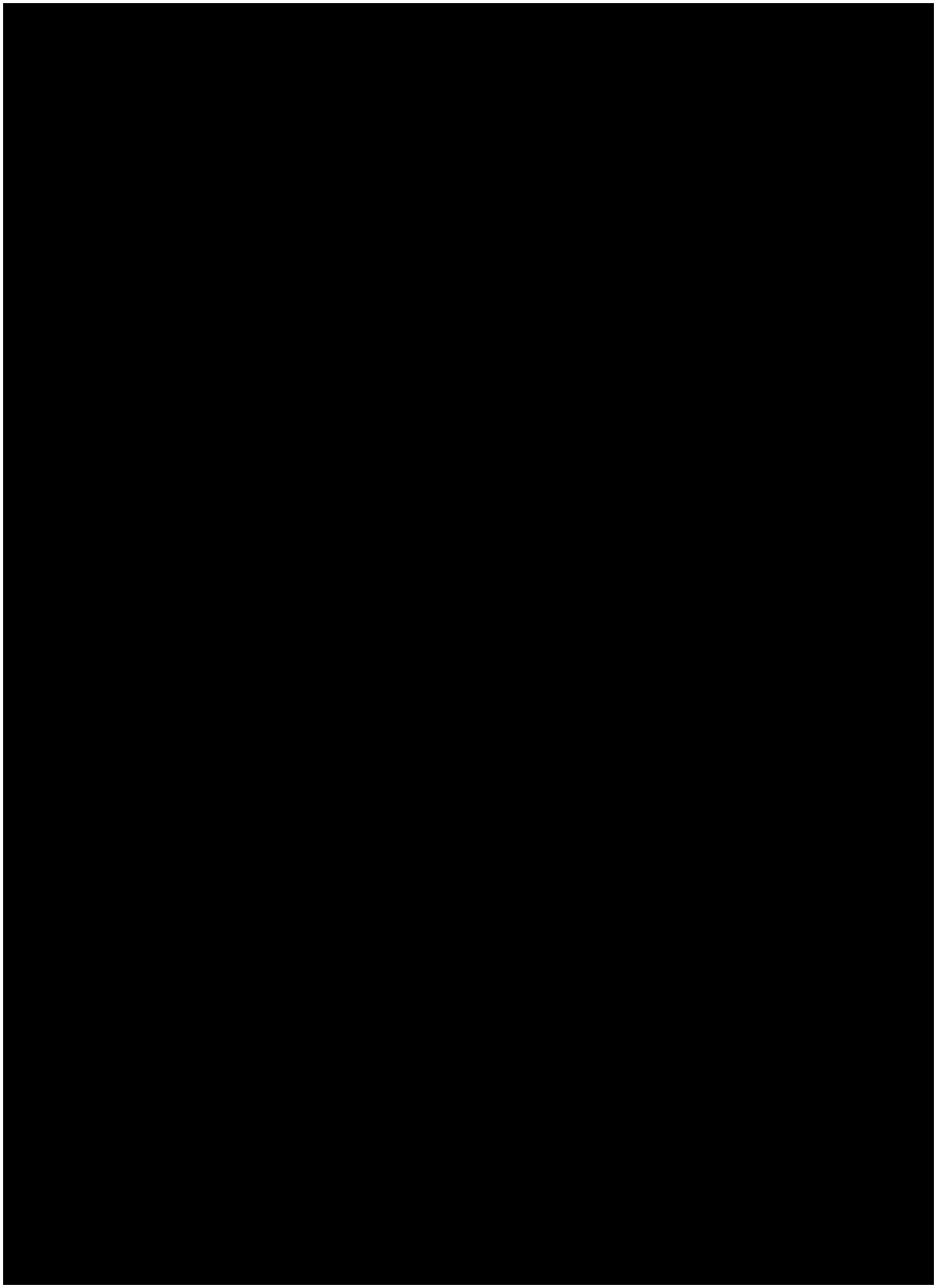


Table 53 BHMs statistical fit – PFS

Parametric model	DIC
Exponential	[redacted]
Weibull	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Abbreviations: BHM, Bayesian hierarchical model; DIC, deviance information criterion; OS, overall survival.	

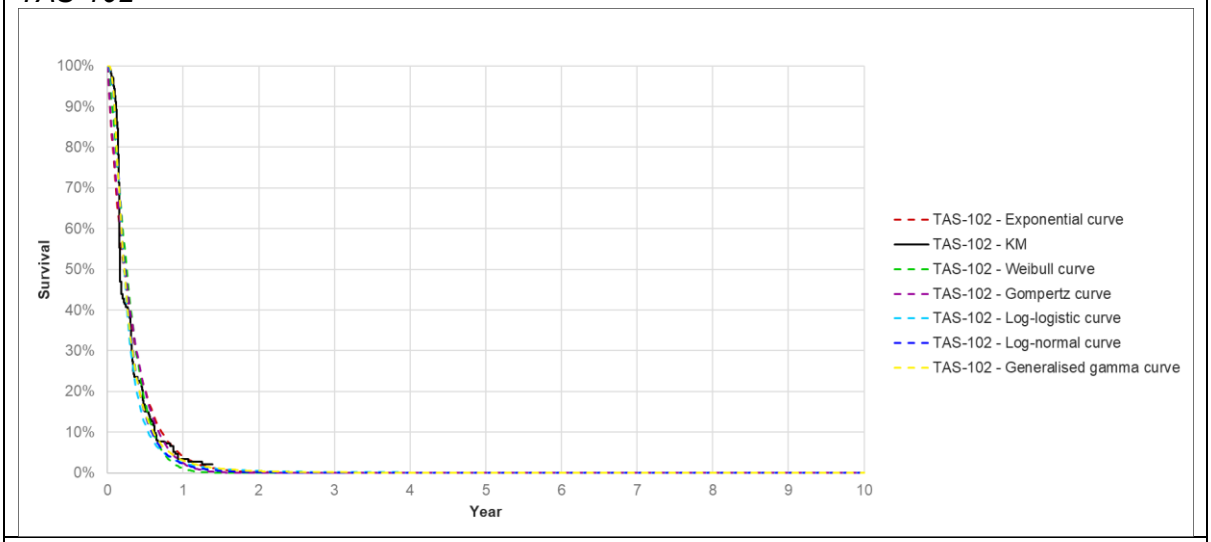
B.3.3.6.2 Comparators

For comparator treatments, individual fitted curves for each tumour site were chosen as the base case. Comparator extrapolations beyond the observed follow-up period of the trial and predicted survival are given in Figure 30, Figure 31, Figure 32, Figure 33 and Figure 34 and for each tumour site. Respective AIC/BIC values are given in Table 54, Table 55, Table 56, Table 57 and Table 58.

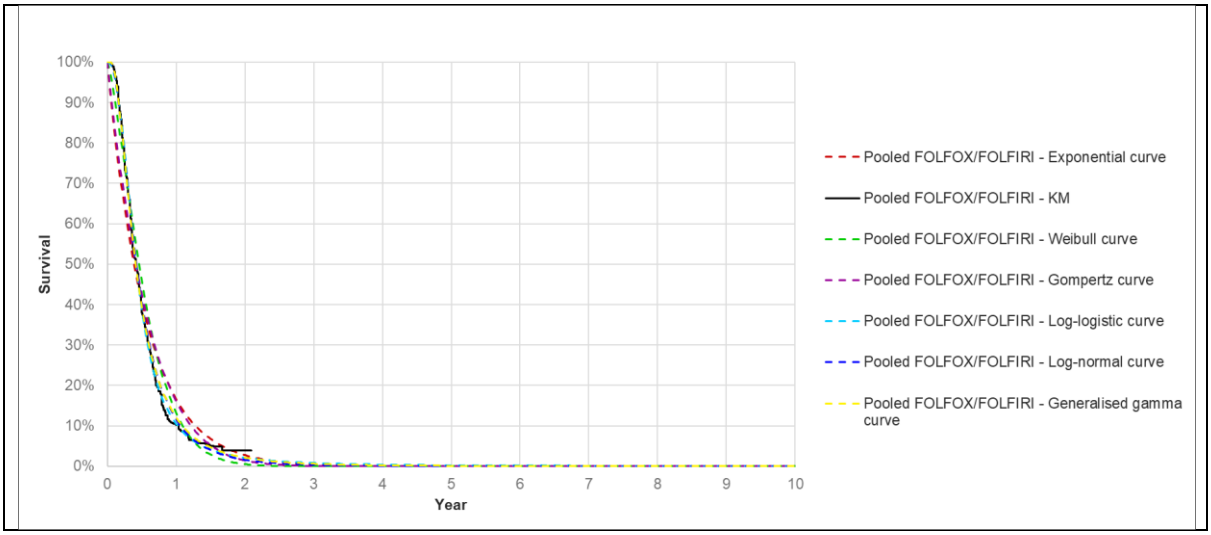
Table 59 summarizes the best fitting curves for each comparator for each tumour site. Base case curves were selected using statistical and visual fits, given the maturity of the data and small differences between the available extrapolations. Clinical opinion and validation with published sources were also considered.

Figure 30 Standard parametric modelling – CRC – PFS

TAS-102



Pooled FOLFOX/FOLFIFI



Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; KM, Kaplan–Meier; PFS, progression-free survival.

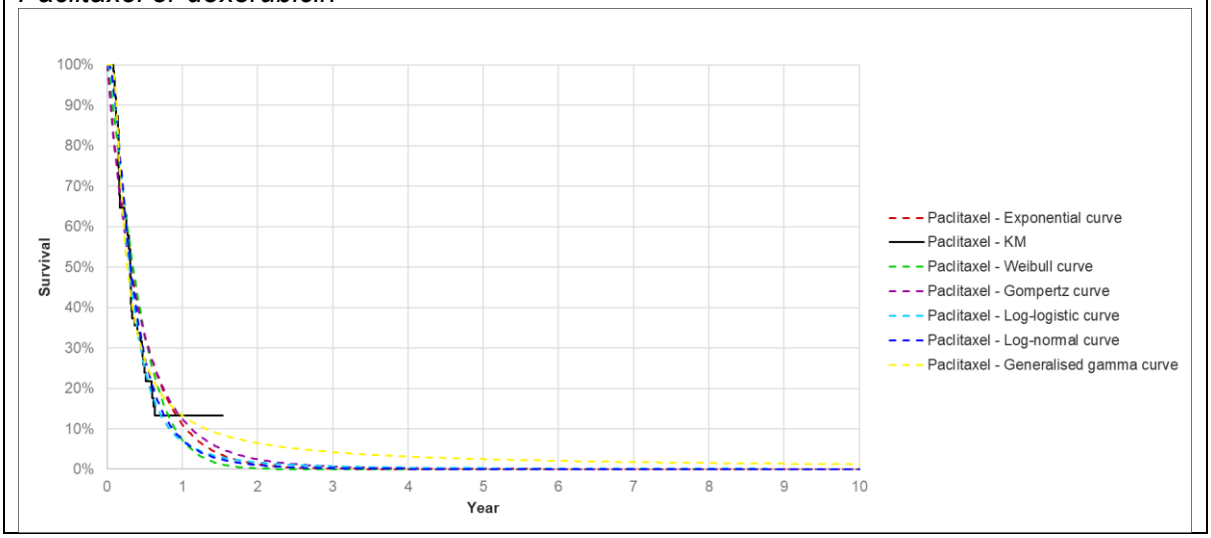
Table 54 Best fitting curves – CRC – PFS

Parametric model	TAS-102		Pooled FOLFOX/FOLFIRI	
	AIC	BIC	AIC	BIC
Exponential	3413.97	3418.25	5532.31	5536.83
Weibull	3344.92	3353.48	5429.82	5438.87
Gompertz	3408.59	3417.15	5524.97	5534.01
Log-logistic	3222.72	**3231.28**	**5276.54**	**5285.59**
Log-normal	3228.46	3237.02	5288.41	5297.46
Generalized gamma	**3222.44**	3235.28	5286.27	5299.84

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CRC, colorectal cancer; PFS, progression-free survival.

Figure 31 Standard parametric modelling – Endometrial cancer – PFS

Paclitaxel or doxorubicin



Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival.

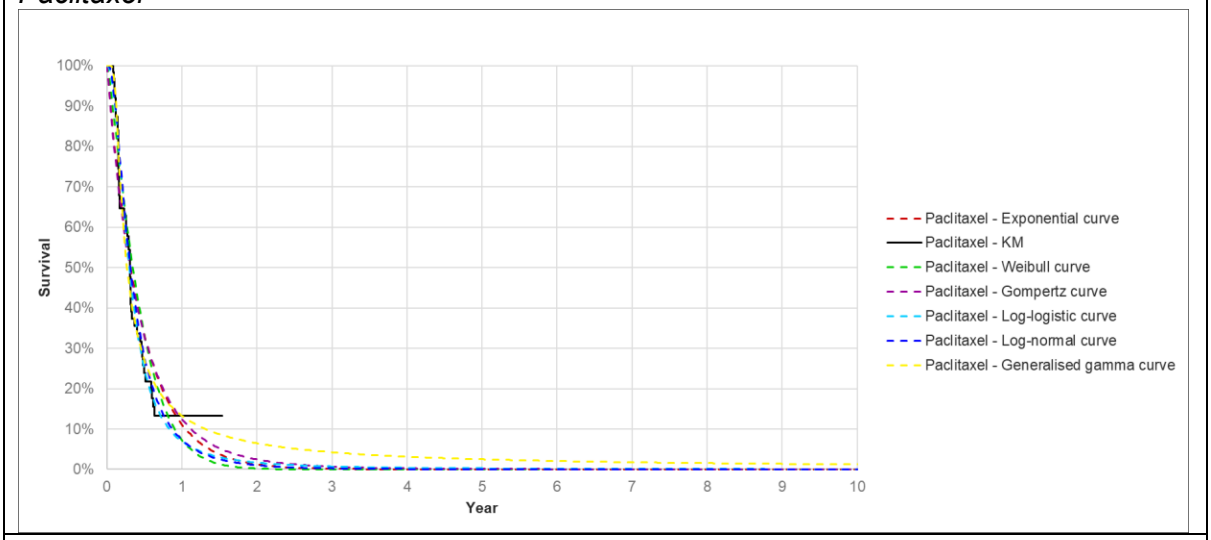
Table 55 Best fitting curves – Endometrial cancer – PFS

Parametric model	Paclitaxel or doxorubicin	
	AIC	BIC
Exponential	418.96	421.13
Weibull	416.98	421.33
Gompertz	420.70	425.05
Log-logistic	400.06	404.41
Log-normal	399.73	404.08
Generalized gamma	**391.74**	**398.26**

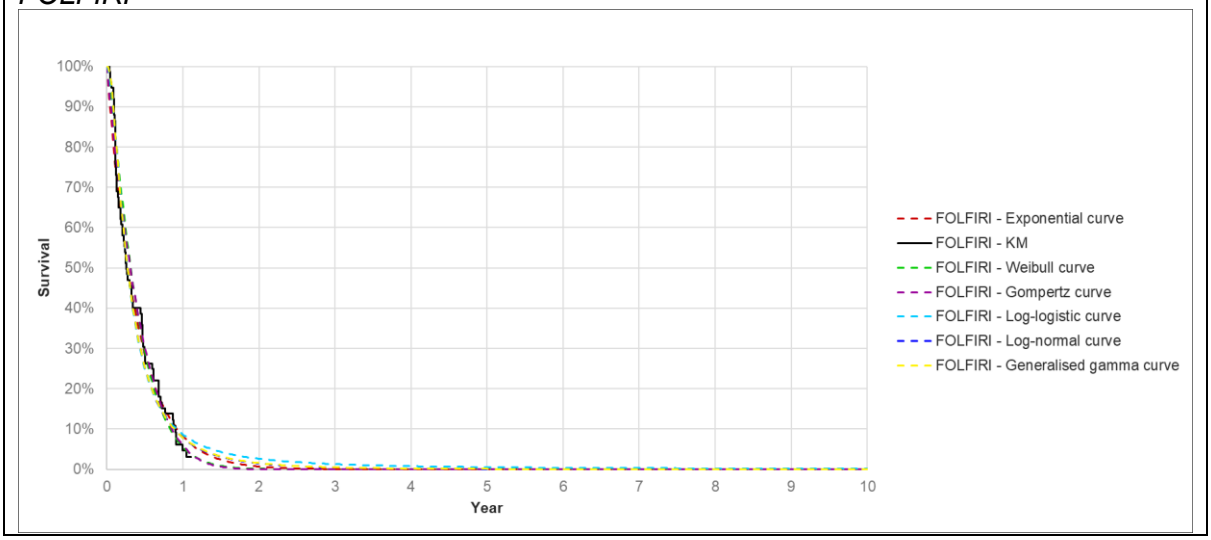
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Notes: Efficacy inputs for paclitaxel and doxorubicin are the same for both treatments in the cost-effectiveness model.

Figure 32 Standard parametric modelling – Gastric cancer – PFS

Paclitaxel



FOLFIRI



Abbreviations: FOLFIRI, folinic acid, fluorouracil and irinotecan; KM, Kaplan–Meier; PFS, progression-free survival.

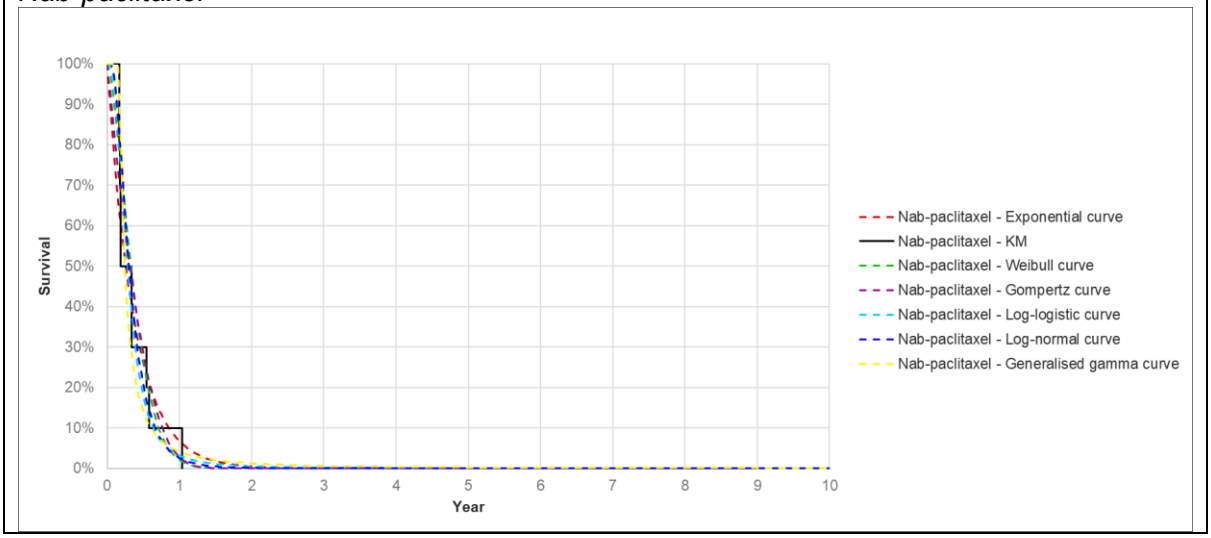
Table 56 Best fitting curves – Gastric cancer – PFS

Parametric model	Paclitaxel		FOLFIRI	
	AIC	BIC	AIC	BIC
Exponential	89.66	90.14	567.30	569.62
Weibull	91.63	92.60	564.67	569.31
Gompertz	91.14	92.11	567.28	571.92
Log-logistic	88.46	89.43	563.76	568.39
Log-normal	88.12	89.09	**559.30**	**563.93**
Generalized gamma	**84.39**	**85.84**	561.30	568.25

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; FOLFIRI, folinic acid, fluorouracil and irinotecan; PFS, progression-free survival.

Figure 33 Standard parametric modelling – Small intestinal cancer – PFS

Nab-paclitaxel



Abbreviations: KM, Kaplan–Meier; PFS, progression-free survival.

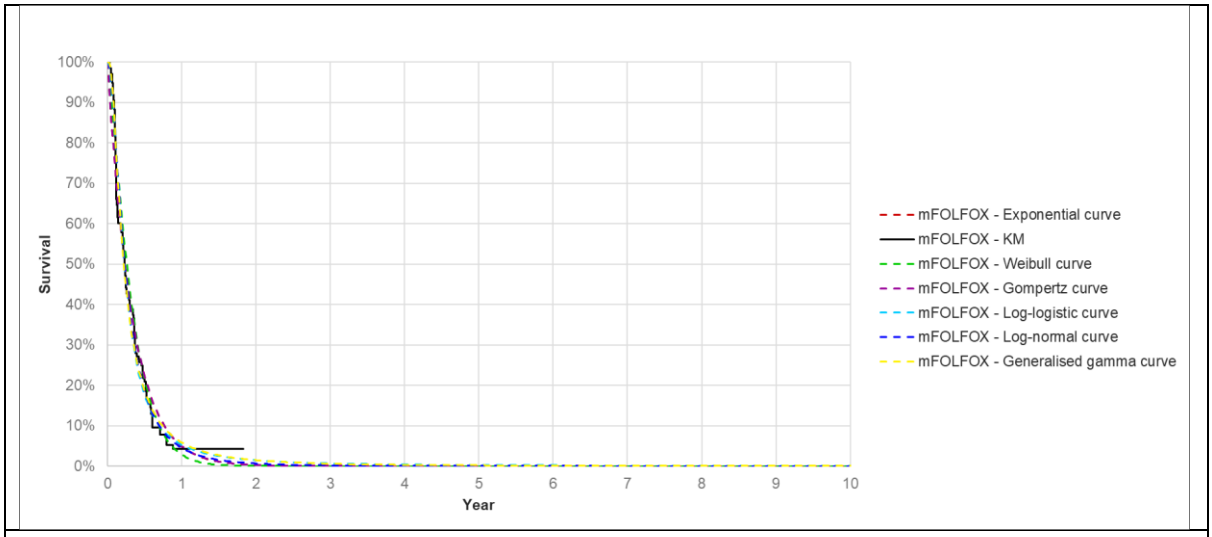
Table 57 Best fitting curves – Small intestine cancer – PFS

Parametric model	Nab-paclitaxel	
	AIC	BIC
Exponential	81.29	81.60
Weibull	80.42	81.03
Gompertz	82.10	82.70
Log-logistic	78.52	79.12
Log-normal	77.81	78.42
Generalized gamma	**71.55**	**72.45**

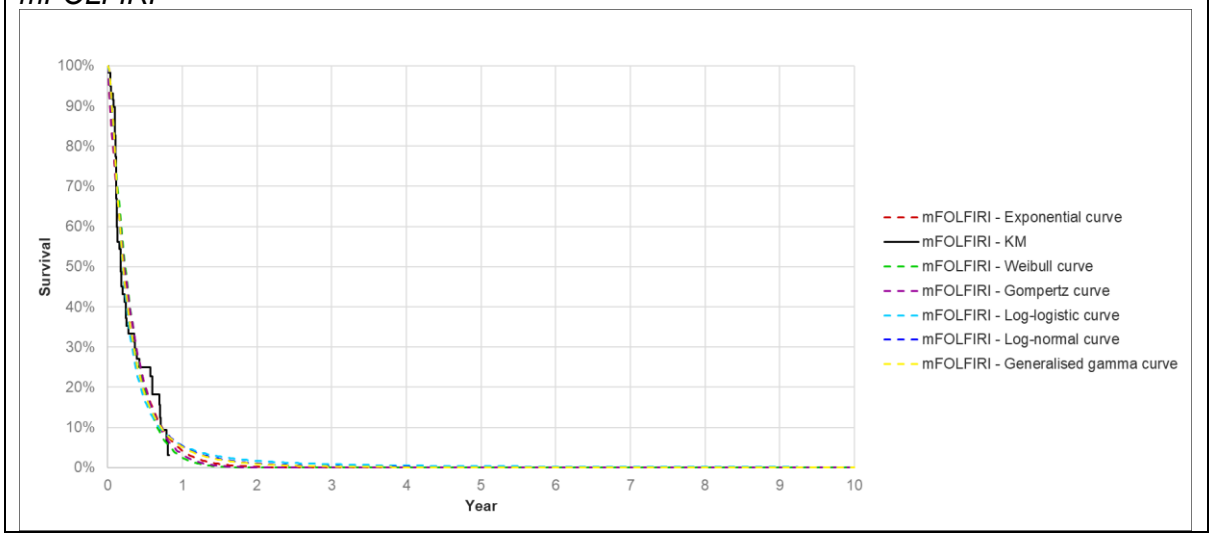
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Figure 34 Standard parametric modelling – Cholangiocarcinoma – PFS

mFOLFOX



mFOLFIRI



Abbreviations: mFOLFIRI, modified folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; KM, Kaplan–Meier; PFS, progression-free survival.

Table 58 Best fitting curves – Cholangiocarcinoma – PFS

Parametric model	mFOLFOX		mFOLFIRI	
	AIC	BIC	AIC	BIC
Exponential	964.23	967.15	374.52	376.59
Weibull	959.36	965.20	374.82	378.98
Gompertz	966.23	972.07	376.35	380.51
Log-logistic	941.13	946.97	369.82	373.97
Log-normal	936.30	**942.14**	**369.40**	**373.56**
Generalized gamma	**936.30**	945.06	371.39	377.62

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFIRI, modified folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; PFS, progression-free survival.

Table 59 Summary of best fitting curves from ITC – PFS

Comparator	AIC	BIC	Base Case
CRC			
TAS-102	Generalized gamma	Log-logistic	Log-logistic
Pooled FOLFOX/FOLFIRI	Log-logistic	Log-logistic	Log-logistic
Endometrial			
Paclitaxel or doxorubicin	Generalized gamma	Generalized gamma	Gompertz
Gastric			
Paclitaxel	Generalized gamma	Generalized gamma	Gompertz
FOLFIRI	Log-normal	Log-normal	Gompertz
Small intestine			
Nab-paclitaxel	Generalized gamma	Generalized gamma	Weibull
Cholangiocarcinoma			
mFOLFOX	Generalized gamma	Log-normal	Log-normal
mFOLFIRI	Log-normal	Log-normal	Log-normal

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CRC, colorectal cancer; (m)FOLFIRI, (modified) folinic acid, fluorouracil and irinotecan; mFOLFOX, (modified) folinic acid, fluorouracil and oxaliplatin; ITC, indirect treatment comparison; PFS, progression-free survival.
Notes: The best statistical fit was used to inform base case selections, except where curves resulted in an implausibly long tail for comparator therapies. In these instances, visual fit and clinical plausibility took precedence.

B.3.3.6.3 Summary of PFS base case

The below figures show the selected base case curves for both pembrolizumab and comparators for each tumour site of interest. Visually, the base case curve does not fit the observed pembrolizumab PFS data very well: the CRC curve appears to overestimate PFS from 6 to 18 months and thereafter underestimates PFS; observed plateaus in KM data for CRC, gastric and small intestine tumour sites are not captured in the extrapolations; and there is apparent underestimation of endometrial PFS. Therefore, the selection is considered to be conservative. Results are insensitive to alternative comparator PFS selections and show a sustained PFS benefit for pembrolizumab compared with chemotherapy for each tumour site (consistent with clinical expectations), which is reflected in the cost-effectiveness results.

Figure 35 Selected base case curve – CRC – PFS

Figure 36 Selected base case curve – Endometrial – PFS

Figure 37 Selected base case curve – Gastric – PFS

Figure 38 Selected base case curve – Small intestine – PFS

Figure 39 Selected base case curve – Cholangiocarcinoma – PFS

Abbreviations: CRC, colorectal cancer; (m)FOLFIRI, (modified) folinic acid, fluorouracil and irinotecan; (m)FOLFOX, (modified) folinic acid, fluorouracil and oxaliplatin; KM, Kaplan–Meier; PFS, progression-free survival.

B.3.3.7 Time to treatment discontinuation

B.3.3.7.1 Pembrolizumab

In the base-case analysis for pembrolizumab, TTD KM data from the KN-164 and KN-158 clinical trials were used. TTD data were not combined across tumour sites. TTD KM plots are presented in Figure 40 for pembrolizumab. The data correspond to the 19 February 2021 cutoff date for KN-164 and the 15 October 2021 cutoff date for KN-158.

The model incorporates functionality to ensure that patients receive a maximum of 35 costed cycles of treatment with pembrolizumab, consistent with KN-164 and KN-158 clinical trial protocols and the approved pembrolizumab label.(41) The implementation of this functionality within the economic analysis is consistent with assumptions applied in previous NICE appraisals (TA709, TA531 and TA557).

Figure 40 Pembrolizumab time on treatment (KN-164, KN-158)

B.3.3.7.2 Comparators

Published TTD KM data for comparator therapies were largely unavailable (either unreported in the published literature or redacted in previous HTA submissions). Where median time on treatment (ToT) data were reported, an exponential distribution was fitted to the reported median ToT estimate. For the remaining comparators, alternative methods were required to model comparator TTD. Feedback from UK clinical experts suggested that, for several comparators, TTD would be expected to be equivalent to PFS; this assumption was therefore used where appropriate. A summary of selections in the base case for the comparators for each tumour site are given in Table 60.

Table 60 Summary of selected curves – TTD

Comparator	Base case
CRC	
TAS-102	TTD equal to PFS
Pooled FOLFOX/FOLFIRI	Exponential fitted to the median ToT
Endometrial	
Paclitaxel	TTD equal to PFS
Doxorubicin	TTD equal to PFS
Gastric	
Paclitaxel	TTD equal to PFS
FOLFIRI	TTD equal to PFS
Small intestine	
Nab-paclitaxel	Exponential fitted to the median ToT
Cholangiocarcinoma	
mFOLFOX	Exponential fitted to the median ToT
mFOLFIRI	Exponential fitted to the median ToT
Abbreviations: CRC, colorectal cancer; (m)FOLFIRI, (modified) folinic acid, fluorouracil and irinotecan; (m)FOLFOX, (modified) folinic acid, fluorouracil and oxaliplatin; PFS, progression-free survival; ToT, time on treatment; TTD, time to treatment discontinuation	

B.3.3.8 Background mortality

General population mortality was estimated from the most recent version of the national life tables for England and Wales, published by the ONS.(68) General population mortality was included to ensure that the modelled mortality risk did not fall below the general population mortality risk at any given age. To do so, the hazards of PFS and OS events were set to always equal or exceed the general population mortality hazard.

General population mortality was calculated separately for each tumour site dependent on the baseline age and gender distribution observed in the KN-164 or KN-158 clinical trials (see Section B.3.3.1).

B.3.3.9 Treatment effect waning

The clinical benefit of immunotherapies such as pembrolizumab has been shown to extend beyond a patient completing their treatment due the mechanism of action, but the longevity of this effect is uncertain.

The treatment effect represents the degree to which the hazards of survival differ between an intervention and comparator. In extrapolating the fitted curves, the treatment effect is the difference that emerges between the modelled treatment arms. When this difference implies an unduly lengthy or persistent treatment effect, treatment effect waning is a mechanism by which the hazards can be equalized between treatments over time. This is done by assuming comparator hazards of survival for the treatment arm after a plausible time point.

To implement treatment effect waning, the economic analysis allows a time at which treatment effect waning starts and ends to be specified, as well as the proportion of patients to which it applies. In each case, a comparator against which the treatment waning is applied as a reference must be selected, which means selecting the treatment that acts as the baseline hazard function. In the case that the start and end date of treatment waning is selected as being the same time, the pembrolizumab hazard is assumed to be replaced by the chosen comparator hazard immediately. If there is a difference between the start and end date, the model uses linear interpolation to model a gradual decline of the pembrolizumab hazard towards the chosen comparator hazard. This approach is considered more clinically plausible as it is unlikely that the treatment effect would be lost immediately, but more likely decrease over a period of time.

The mechanism of action of PD-1 inhibitors such as pembrolizumab enable cytotoxic CD8+ T-cells to avoid an exhausted state, thereby allowing them to keep the disease in a state of cancer-immune equilibrium, which can potentially be maintained for up to several decades even in the absence of continued therapy.(80, 81) As noted

previously, clinical opinion suggested that a group of functionally cured patients is established at around 5 years after treatment initiation across tumour sites, with a probability of death consistent with that of age-adjusted general population mortality. The assumption of treatment effect waning is contradictory to this expectation.

Historic trials of pembrolizumab in the metastatic setting have repeatedly shown sustained treatment effects, consistent with a functionally cured group:

- KEYNOTE-006 represents the longest follow-up (median 7 years) from a phase 3 trial of anti-PD-1/L1 therapy for advanced melanoma available to date. The long-term outcomes observed in KEYNOTE-006 with patients treated up to 2 years is generally consistent with those observed in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule(82-84)

- In KEYNOTE-024 (a trial of pembrolizumab monotherapy in PD-L1 ≥50% NSCLC), there was no narrowing of the relative benefit of pembrolizumab monotherapy versus chemotherapy through 5 years of follow-up, despite a high degree of crossover to pembrolizumab among those who progressed on chemotherapy(85-87)

Treatment effect waning is conventionally applied to reflect a possible reduction in treatment effect due to completing treatment (or discontinuation). However, the majority of patients in the KEYNOTE-158 and KEYNOTE-164 trials have completed pembrolizumab treatment during the observed period – KM curves reflect at least 3 years of efficacy post-discontinuation - and so the impact of discontinuation has already been largely accounted for in the estimation of the hazard functions of the fitted parametric models. Additionally, applying a plausible treatment effect waning scenario for pembrolizumab is challenging; due to the very severe survival outcomes associated with comparator chemotherapies, nearly all patients in the comparator arm were already dead at the time treatment effect waning could have plausibly commenced for pembrolizumab. Considering both clinical plausibility and technical limitations, applying treatment effect waning functionality results in a highly conservative and most improbable prediction of long-term survival outcomes for patients treated with pembrolizumab.

However, in order to reflect the recommendations of EAGs in previous appraisals of pembrolizumab and present a conservative estimate of the economic value of pembrolizumab, treatment waning was applied in the base case. Treatment effect waning is implemented, whereby waning occurs between 7 and 9 years (i.e. begins at 7 years from start of treatment and 5 years from maximum treatment duration). The starting point for waning of 7 years was selected because the KM curves for pembrolizumab, in all tumour sites, extend beyond 5 years and therefore a time point of 2 years past the end of the observed trial period was selected for initiation of treatment effect waning (which has become a common convention in oncology appraisals).

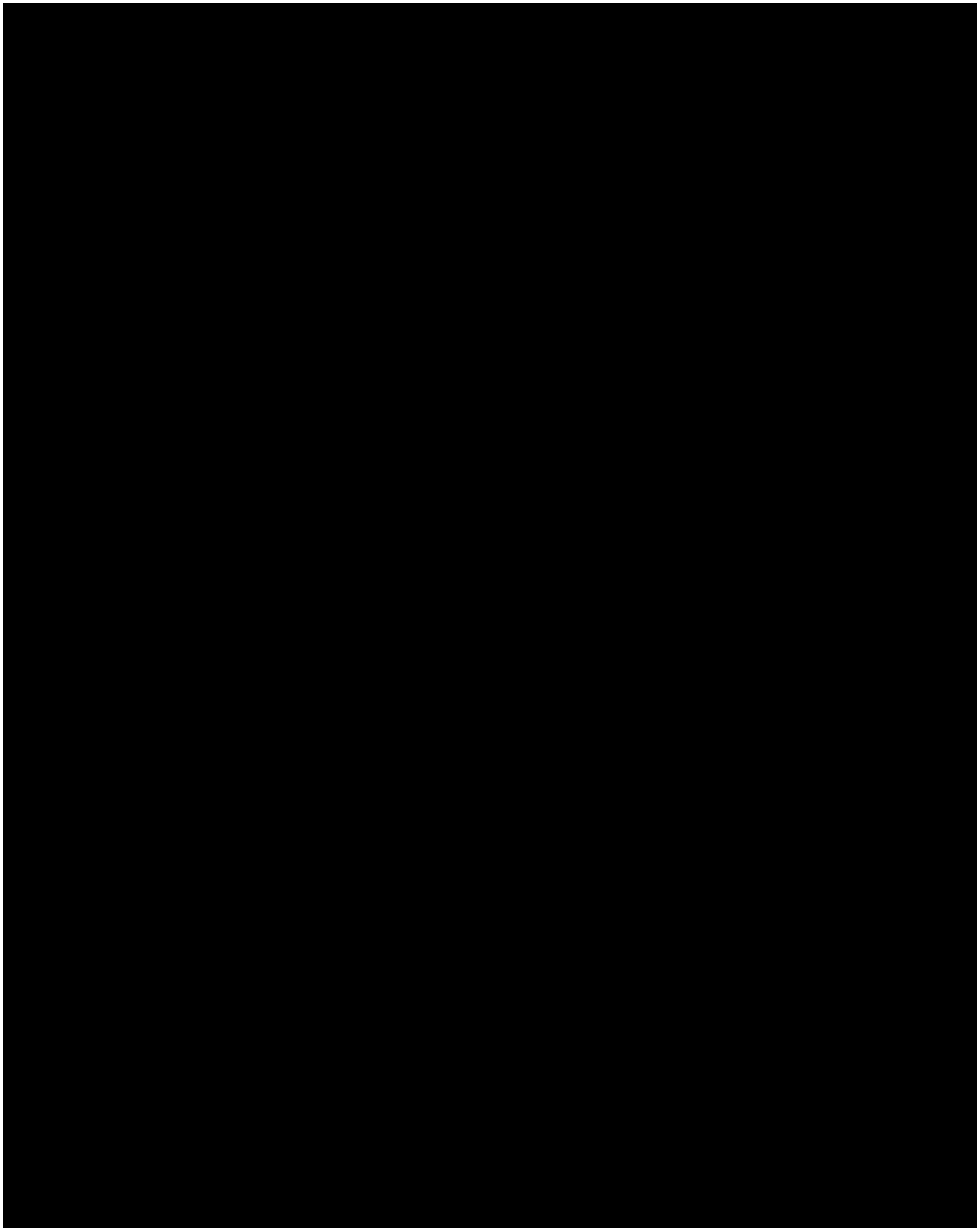
Waning is applied to all surviving pembrolizumab patients and a summary of the comparators used to inform the baseline hazard function is provided in Table 61. The impact of treatment effect waning on pembrolizumab OS is shown in Figure 41. For the reasons mentioned above, the results of the base case analysis should be interpreted with caution and considered as a likely 'worst case'. It is clear that for some tumour sites, especially gastric and small intestine cancer that the analysis is more consistent with assuming all pembrolizumab die at the end of the waning period rather than the treatment effect being removed.

Table 61 Treatment effect waning baseline comparator

Treatment	Treatment effect waning baseline
CRC	Pooled FOLFOX/FOLFIRI
Endometrial	Paclitaxel
Gastric	Paclitaxel
Small intestine	Nab-paclitaxel
Cholangiocarcinoma	mFOLFOX

To show the impact of treatment effect waning on cost-effectiveness results, a scenario removing the application of pembrolizumab treatment effect waning was explored. In all other scenarios treatment effect waning for pembrolizumab was retained.

Figure 41 BHM – Pembrolizumab OS including treatment effect waning



Abbreviations: BHM, Bayesian hierarchical modelling; CRC, colorectal cancer; KM, Kaplan–Meier; OS, overall survival.
Notes: The impact of waning is derived based on the comparator hazard rather than comparator survival. Therefore, even if a comparator has a negligible proportion of patients remaining alive, due to the shape of the hazard function the probability of death may still be relatively low. For example, this manifests in different magnitudes of change in the pembrolizumab survival curve when comparing CRC with small intestine.

B.3.3.10 Adverse event probabilities

The model captures the health and cost implications of treatment-related adverse events (AEs). The incidence of AEs associated with pembrolizumab treatment was informed by KN-164 (for CRC only) and KN-158 (for other tumour sites).(38, 41) Grade 3+ AEs with an incidence of 1% or greater were included for pembrolizumab, while only grade 3+ AEs with an incidence of 3% or greater were included for comparators. A lower threshold of 1% was used for pembrolizumab to ensure the impact of AEs was captured in all tumour sites. Including a higher incidence threshold for comparator AEs was considered a conservative but pragmatic assumption to avoid the total number of AEs included in the model becoming excessively large. The model includes functionality for AEs to be measured by pooled data across tumour sites or as disaggregated data by each individual tumour site. Applicable AEs observed for pembrolizumab are shown in Table 62.

For comparator AE incidence rates used in the model, data were sourced from studies identified by the clinical SLR, using where possible the same studies as were used to inform survival outcomes. For all other comparators included in the model, AE incidence rates are recorded in Appendix K.

AEs costs can be applied either on a per-cycle basis or one-off at model start. AE rates and costs applied on a per-cycle basis are informed by the percentage of patients experiencing each specific event, converted to a per-cycle (weekly) rate and observed across the mean ToT for the safety population derived from each treatment's respective clinical trials or assumption. Mean ToT for the CRC, endometrial, gastric, small intestine and cholangiocarcinoma tumour sites for pembrolizumab is 370, 398, 324, 475 and 362 days, respectively (Section B.2.6). Mean observed ToT for the safety population for comparators are provided in Appendix K.

Table 62 AE incidence rates (≥ 1%) – pembrolizumab

Adverse event	n	n/patient	Weekly rate
CRC (n = 124)			
Alanine aminotransferase increase	2	1.6%	0.0003
Fatigue	2	1.6%	0.0003
Lipase increase	2	1.6%	0.0003
Pancreatitis	2	1.6%	0.0003

Adverse event	n	n/patient	Weekly rate
Endometrial (n = 83)			
Colitis	1	1.2%	0.0002
Enterocolitis	1	1.2%	0.0002
Lymphocyte count decreased	2	2.4%	0.0005
Neutrophil count decreased	1	1.2%	0.0002
Transaminases increased	2	2.4%	0.0005
White blood cell count decreased	1	1.2%	0.0002
Hyperglycaemia	2	2.4%	0.0005
Hypophosphataemia	1	1.2%	0.0002
Pain in extremity	1	1.2%	0.0002
Pemphigoid	1	1.2%	0.0002
Rash	1	1.2%	0.0002
Gastric (n = 51)			
Myocarditis	1	2.0%	0.0004
Hyperthyroidism	1	2.0%	0.0004
Diarrhoea	1	2.0%	0.0004
Hepatitis	1	2.0%	0.0004
Hypertransaminasaemia	1	3.9%	0.0008
Aspartate aminotransferase increased	2	2.0%	0.0004
Blood alkaline phosphatase increased	1	2.0%	0.0004
Blood creatine phosphokinase increased	1	2.0%	0.0004
Gamma-glutamyl transferase increased	1	2.0%	0.0004
Hyperglycaemia	1	2.0%	0.0004
Arthritis	1	3.9%	0.0008
Muscular weakness	1	2.0%	0.0004
Guillain-Barre syndrome	2	2.0%	0.0004
Pneumonitis	1	2.0%	0.0004
Small intestine (n=27)			
Hepatitis	1	3.7%	0.0007
Hypophosphatasaemia	1	3.7%	0.0007
Pneumonitis	1	3.7%	0.0007
Respiratory failure	1	3.7%	0.0007
Cholangiocarcinoma (n=22)			
Alanine aminotransferase increase	1	4.5%	0.0009
Arthritis reactive	1	4.5%	0.0009
Fatigue	1	4.5%	0.0009
Abbreviations: CRC, colorectal cancer.			

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQL data were collected in the KN-158 trial using EQ-5D-3L questionnaires and the UK value set applied.(88) Specifically, the data were collected in the FAS

population, which consists of all participants who have received treatment and have at least one PRO assessment available. No HRQL data were collected in the KN-164 trial.

In KN-158, PROs were assessed at every cycle for the first four cycles, then every three cycles until 9 months, then every four cycles until PD while the participant was receiving study treatment, at the treatment discontinuation visit, and at the 30-day safety follow-up visit. If the treatment discontinuation visit occurred 30 days after the last dose of study treatment, at the time of the mandatory safety follow up visit, PROs were not repeated. Patients therefore had a maximum of two (and possibly one) observation at or post-discontinuation.

A total of 1,148 records from 168 patients from KN-158 were available to inform patient HRQL. Of these, 157 patients had EQ-5D-3L measured beyond baseline, and 11 patients only had baseline EQ-5D-3L measures.

Table 63 and Table 64 show the summary EQ-5D-3L utility data by tumour site and by time to death.

Table 63 KN-158 EQ-5D-3L utility data summary by tumour site

Tumour site	Number of observations	Number of patients	Mean (SD)
Endometrial	[redacted]	[redacted]	[redacted]
Gastric	[redacted]	[redacted]	[redacted]
Small intestine	[redacted]	[redacted]	[redacted]
Cholangiocarcinoma	[redacted]	[redacted]	[redacted]
Abbreviations: SD, standard deviation			

Table 64 KN-158 EQ-5D-3L utility data summary by time to death

Tumour site	Number of observations	Mean (SD)
<30 days	[redacted]	[redacted]
30-89 days	[redacted]	[redacted]
90-179 days	[redacted]	[redacted]
180-359 days	[redacted]	[redacted]
360+ days	[redacted]	[redacted]
Abbreviations: SD, standard deviation		

Three different approaches to categorize the utility data were considered:

- Utility values by health state (e.g. progression-free and PD)
- Utility values by health state and tumour site
- Utility values based on patient time to death

Since EQ-5D-3L information was collected repeatedly over time, observations tend to be correlated across time points, resulting in non-independence of utility estimates. To account for this, all three approaches were derived by fitting linear mixed-effects regression models to account for repeated measures.

B.3.4.2 Mapping

As EQ-5D-3L data were collected within the KN-158 clinical trial, no mapping methods were required for the estimation of HRQL data.

B.3.4.3 Health-related quality-of-life studies

The KN-164 clinical trial did not collect HRQL data. Therefore, utility values for CRC were identified from relevant HRQL data identified by the SLR described in [redacted]

The SLR identified a publication by Grothey et al. (2013) (67), which reported on the outcomes of a multicentre, randomized, Phase III clinical trial assessing regorafenib monotherapy vs placebo in previously treated mCRC. EQ-5D-based utility values, by treatment group and treatment status were one of the outcomes of interest; specifically, the following utility values were reported (no measures of variation around the mean were reported):

- 0.73 in the regorafenib group
- 0.74 in the placebo group at baseline
- 0.59 in both groups at the end of treatment

Given the lack of data from the KEYNOTE-164 trial to inform the CRC tumour site-specific utility values, the values of 0.73, 0.74, and 0.59 reported in Grothey et al. (2013) (67) were used in the base case to inform HRQL for the PFS on treatment, PFS off treatment, and the PD (on and off treatment) states, respectively.

B.3.4.4 Adverse reactions

AE disutilities associated with MSI-H/dMMR solid tumours are not included in the base case as they are assumed to be captured within the EQ-5D utility values; incorporating an additional disutility could be considered double counting.

Scenario analyses conducted to assess the impact of including AE disutilities in the cost-effectiveness analysis are explored in Section B.3.11.3.

Table 65 AE disutility per patient, per treatment, per tumour site

Tumour site	Treatment	Total QALY loss per patient
CRC	Pembrolizumab	-0.0001
	TAS-102	-0.0017
	Pooled FOLFOX/FOLFIRI	-0.0004
Endometrial	Pembrolizumab	-0.0003
	Paclitaxel	-0.0016
	Doxorubicin	-0.0016
Gastric	Pembrolizumab	-0.0006
	Paclitaxel	-0.0019
	FOLFIRI	-0.0019
Small intestine	Pembrolizumab	-0.0003
	Nab-paclitaxel	-0.0005
Cholangiocarcinoma	Pembrolizumab	-0.0002
	mFOLFOX	-0.0011
	mFOLFIRI	-0.0010

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The model allows for utility values by health state and time to death to be explored. For tumour sites included in KN-158, the time-to-death utility approach was selected as the base case to accurately depict the declining quality of life patients may experience as they move closer to death, as presented visually in Figure 42. The health state approach does not account for variation in quality of life from the time of progression through to terminal care. Although all approaches were considered plausible, the time-to-death approach was preferred by clinical experts during consultation at an advisory board. This is because the utility trends associated with the time-to-death approach are deemed more reflective of patient HRQL outcomes for pembrolizumab, which is associated with long survival tails and a functionally

cured proportion.(1) The time-to-death utility values used in the model are presented in Table 66.

Figure 42 KN-158 time-to-death utility values, pooled by tumour site

Table 66 Summary of base case utility values analysis for endometrial, gastric, small intestine, and cholangiocarcinoma tumour sites

Time to death	Mean utility value
360+ days	[redacted]
180-159 days	[redacted]
90-179 days	[redacted]
30-89 days	[redacted]
<30 days	[redacted]

In the absence of comparator utility estimates, utilities were assumed to be the same across treatment regimens. This was considered a conservative assumption given the known toxicity of comparator chemotherapy regimens and that AE disutilities were not applied in the base case.

For CRC, utility values were based on Grothey et al. (2013)(67), which was identified via the SLR. This was necessary as KN-164 did not collect HRQL data. Given the reliance on the literature to source CRC utility values, these were limited by the data available; therefore, utility values by progression and treatment status are used rather than by time to death. These are presented in Table 67.

Table 67 Summary of selected utility values for CRC

	Mean utility value
Progression free, on treatment	0.73
Progression free, off treatment	0.74
Progressed disease	0.59

Health state utilities were also adjusted within the model to account for the age-matched general population using a utility multiplier derived from Hernandez Alava, as recommended in the latest NICE reference case.(88) This is necessary given that the short-term data collected in KN-158 are unlikely to capture the age-related decline in HRQL over time.

The health state utility approach is also explored in scenario analyses (Section B.3.11.3) and a summary of health state utilities by tumour site provided in Table 68.

Table 68 Utility values by progression status and tumour site – scenario analysis

Tumour site	Progression-free	Progressed
Endometrial	0.721	0.667
Gastric	0.708	0.654
Small intestine	0.814	0.737
Cholangiocarcinoma	0.805	0.702

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

An SLR for published cost and healthcare resource identification, measurement and valuation data in second-line or later settings to treat MSI-H/dMMR advanced/metastatic solid tumours was run alongside the searches for economic evaluation and HRQL data noted in Sections B.3.1 and B.3.4.3. This is described in Appendix G.

Relevant studies were identified in the SLR that were used to inform costing inputs and/or assumptions. Most notably, relevant NICE appraisals that were identified through the SLR and through the separate targeted searches, described in Section B.3.1, were used to inform health state unit costs and resource use. This is further described in Section B.1.1.1.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition and administration costs

B.3.5.1.1.1 Pembrolizumab

The dosing schedule for pembrolizumab in the model was consistent with the market authorization and the dose received in KN-158 and KN-164. Specifically, the model uses a fixed pembrolizumab dose of 200 mg, given intravenously every 3 weeks. At list price, the cost per 100 mg vial is £2,630, which equates to £5,260 per administration. This is summarized across Table 69 and Table 70.

The model also accounts for relative dosing intensity (RDI) in the cost of drug acquisition. For pembrolizumab, RDI is derived from the KN-158 and KN-164 trials. Taking this into account, the estimated acquisition cost per administration is presented in Table 71.

Table 69 Pembrolizumab pack cost

Treatment	Pack size	Form	Units	Cost per pack
Pembrolizumab	1	25 mg/ml (vial)	4 ml	£2,630.00

Table 70 Pembrolizumab dosing schedule

Treatment	Prescribed dose per administration	Frequency	Source	Administration method
Pembrolizumab	200 mg	Once every 3 weeks	KN-158 and KN-164 clinical trials	Intravenous

Table 71 Pembrolizumab acquisition cost per administration per tumour site

Treatment	Dose RDI (%)	Source	Cost per administration
CRC	[redacted]	KN-164	[redacted]
Endometrial	[redacted]	KN-158	[redacted]
Gastric	[redacted]	KN-158	[redacted]
Small intestine	[redacted]	KN-158	[redacted]
Cholangiocarcinoma	[redacted]	KN-158	[redacted]

B.3.5.1.1.2 Standard of care

The SoC treatment arm is applied as a basket of comparators, which is informed by available market share data within each tumour site. When the SoC treatment arm is selected as a comparator in the model, each treatment in each tumour site is weighted by its respective market share and combined into one basket to represent the SoC in the observed tumour site. This also allows for comparison to a single blended SoC arm across all tumour sites simultaneously when the pooled tumour site approach is selected in the model. Consensus opinion on market shares was elicited from clinical experts during an advisory board and is presented in Table 72.(1)

Table 72 SoC market shares

Tumour site	**Comparator 1**	**Comparator 2**
CRC	TAS-102	Pooled FOLFOX/FOLFIRI
Market share	30%	70%
Endometrial	Paclitaxel	Doxorubicin
Market share	33.3%	66.7%
Gastric	Paclitaxel	FOLFIRI
Market share	70%	30%
Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	
Market share	100%	
Cholangiocarcinoma	mFOLFOX	mFOLFIRI
Market share	90%	10%
Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin		

Drug acquisition

Dosing schedules and costs for comparator treatments were sourced from the relevant UK specific sources. Specifically, the drugs and pharmaceutical electronic market information tool (eMIT) was used in the first instance as this better reflects the prices paid by hospitals; where eMIT costs were not available, or were not available for the formulation indicated in the SmPC, the Monthly Index of Medical Specialities (MIMS) was used.(89-91) Where multiple options were presented for each dose, the pack providing the cheapest cost per mg was used. Furthermore, it is assumed that the cheapest combination of vials would be selected when preparing each individual dose.

Depending on the drug administration method required, drug wastage is sometimes considered in cost calculations in economic models for IV-administered treatments. The drug wastage method uses the cost of the total number of vials needed to treat a patient based on weight or body surface area (BSA), although patients may only use a portion of a vial. For example, if a patient required a 150 mg dose but the vial pack size for the treatment is 300 mg/ml, the total cost of treatment would be the full cost of the vial and the remaining 150 mg is assumed to be wasted instead of shared between patients, which would lower the total cost of treatment (i.e. vial sharing). In the model, it was assumed for all IV-administered treatments that vials are shared between patients when necessary. This method is a conservative approach as pembrolizumab has a fixed dose, while the majority of IV-administered comparators are based on weight or BSA and would potentially be subject to drug wastage, thus increasing their costs.

For orally administered treatments dosed on patient BSA, specifically TAS-102 (trifluridine/tipiracil), the method of moments was used. A log-normal distribution was assumed and applied to the mean BSA to calculate the average number of tablets per cycle based on the distribution of patients assigned to each BSA category listed on the Lonsurf® SmPC.(92)

The comparator drug acquisition costs and dosing schedules are summarized over Table 73 and Table 74.

As for pembrolizumab, RDI is also considered and, where available, is sourced from published literature and respective drug labels. Taking this into account, the estimated acquisition costs per administration is presented in Table 75.

Table 73 Drug pack cost

Drug	Form	Dose per unit	Units per pack	Pack cost	Source
Trifluridine/Tipiracil	Tablet	6.14 mg, 15 mg	20	£500	BNF(1) [Accessed 21/10/2022]
Folinic acid	50 mg/ml (vial)	400 mg	1	£126.25	BNF [Accessed 19/01/2023]
Oxaliplatin	5 mg/ml (vial)	100 mg	1	£295.63	MIMS [Accessed 19/01/2023]

Fluorouracil (5FU)	25 mg/ml (vial)	2500 mg	1	£4.15	eMIT(3) [Accessed 19/01/2023]
Paclitaxel	6mg/ml (vial)	100 mg	1	£200.35	MIMS [Accessed 20/10/2022]
Doxorubicin	2 mg/ml	200 mg	1	£17.20	eMIT [Accessed 19/01/2023]
Irinotecan	20 mg/ml	100 mg	1	120.25	MIMS [Accessed 20/10/2022]
Regorafenib	Capsule	40 mg	84	£3,744	MIMS [Accessed 20/10/2022]
Bevacizumab	25 mg/ml (vial)	400 mg	1	£810.10	BNF [Accessed 19/01/2022]
Panitumumab	20mg/ml (vial)	100 mg	1	£379.29	MIMS [Accessed 20/10/2022]
Ramucirumab	10 mg/ml (vial)	100 mg	1	£500	eMIT [Accessed 19/01/2023]
Gemcitabine	Powder for solution for infusion vials	1000 mg	1	£8.59	eMIT [Accessed 19/01/2023]
Megestrol	Tablet	160 mg	30	£19.52	MIMS [Accessed 20/10/2022]
Fulvestrant	50 mg/ml (vial)	250 mg	2	£80.03	eMIT [Accessed 04/11/2022]
Tamoxifen	Tablet	20 mg	30	£3.42	eMIT [Accessed 04/11/2022]
Capecitabine	Tablet	500 mg	120	£39.23	eMIT [Accessed 11/11/2022]
Abbreviations: BNF, British National Formulary; eMIT, Drug and pharmaceutical electronic market information tool; MIMS, Monthly Index of Medical Specialties. **Notes:** Form is given as strength per millilitre for vials. The selected packs are those which give the lowest cost per milligram and are therefore used in the model base case.					

Table 74 Dosing schedule

Regimen	Treatment	Dose	Frequency	Source	Administration method
Primary treatments					
TAS-102	Trifluridine/ Tipiracil	35 mg/m^2	Twice daily on days 1 to 5, and days 8 to 12, of a 28 day cycle	Sotelo et al. 2014(93)	Oral
Pooled FOLFOL/FOLFIRI	Folinic acid	400 mg/m^2	Every 2 weeks	Giantonio et al. 2007(49)	IV
	Oxaliplatin	85 mg/m^2	Every 2 weeks		IV
	Fluorouracil	1,000 mg/m^2	Every 2 weeks		IV
Paclitaxel	Paclitaxel	80 mg/m^2	Once a week, for 3 weeks of a 4 week cycle	Makker et al. 2022(56)	IV
Doxorubicin	Doxorubicin	60 mg/m^2	Every 3 weeks		IV
Paclitaxel	Paclitaxel	80 mg/m^2	Once a week, for 3 weeks of a 4 week cycle	Chao et al. 2021(59)	IV
FOLFIRI	Irinotecan	400 mg/m^2	Every 2 weeks	Moehler et al. 2016(57)	IV
	Folinic acid	400 mg/m^2	Every 2 weeks		IV
	Fluorouracil	2,400 mg/mg^2	Every 2 weeks		IV
Nab-paclitaxel	Folinic acid	400 mg/m^2	Every 2 weeks	Giantonio et al. 2007(49)	IV
	Oxaliplatin	85 mg/m^2	Every 2 weeks		IV
	Fluorouracil	1,000 mg/m^2	Every 2 weeks		IV
mFOLFOX	Oxaliplatin	100 mg/m^2	Every 2 weeks	Choi et al. 2021(61)	IV
	Fluorouracil	2,400 mg/m^2	Every 2 weeks		IV
	Folinic acid	100 mg/m^2	Every 2 weeks		IV

Regimen	Treatment	Dose	Frequency	Source	Administration method
mFOLFIRI	Irinotecan	150 mg/m^2	Every 2 weeks	Choi et al. 2021(61)	IV
	Folinic acid	100 mg/m^2	Every 2 weeks		IV
	Fluorouracil	2,400 mg/m^2	Every 2 weeks		IV
Subsequent treatments					
Regorafenib	Regorafenib	160 mg	Every day for 3 week, followed by 1 week off	Li et al. 2015(94)	Oral
Anti-VEGF + chemotherapy	Bevacizumab	10 mg/kg	Every 2 weeks	Giantonio et al. 2007(49)	IV
	Folinic acid	400 mg/m^2	Every 2 weeks		IV
	Oxaliplatin	85 mg/m^2	Every 2 weeks		IV
	Fluorouracil	1,000 mg/m^2	Every 2 weeks		IV
Anti-EGFR + chemotherapy	Panitumumab	6 mg/kg	Every 2 weeks	Peeters et al. 2014(95)	IV
	Irinotecan	180 mg/m^2	Every 2 weeks		IV
	Folinic acid	400 mg/m^2	Every 2 weeks		IV
	Fluorouracil	3,100 mg/m^2	Every 2 weeks		IV
FOLFIRI	Irinotecan	180 mg/m^2	Every 2 weeks	Peeters et al. 2014(95)	IV
	Folinic acid	400 mg/m^2	Every 2 weeks		IV
	Fluorouracil	3,100 mg/m^2	Every 2 weeks		IV

Regimen	Treatment	Dose	Frequency	Source	Administration method
Irinotecan	Irinotecan	180 mg/m^2	Every 2 weeks	Thuss-Patience et al. 2011(96)	IV
Ramucirumab + paclitaxel	Ramucirumab	8 mg/kg	Every 2 weeks	Lorenzen et al 2020(97)	IV
	Paclitaxel	80 mg/m^2	Once a week, for 3 weeks of a 4 week cycle		IV
Gemcitabine + paclitaxel	Gemcitabine	1250 mg/m^2	Every 3 weeks	Colomer et al. 2005(98)	IV
	paclitaxel	150 mg/m^2	Every 2 weeks		IV
Megestrol	Megestrol	160 mg/m^2	Once daily, for 2 weeks, then 1 week off	Eftekhar et al. 2009(99)	Oral
FOLFOX	Folinic acid	400 mg/m^2	Every 2 weeks	Giantonio et al. 2007(49)	IV
	Oxaliplatin	85 mg/m^2	Every 2 weeks		IV
	Fluorouracil	1,000 mg/m^2	Every 2 weeks		IV
Fulvestrant	Fulvestrant	500 mg	Interval of one month with an additional 500 mg dose given two weeks after the initial dose	Faslodex SmPC 2022(100)	Fulvestrant - maintenance
Tamoxifen	Tamoxifen	20 mg	Daily	Tamoxifen SmPC 2022(101)	Oral
Fluorouracil + irinotecan	Fluorouracil	2400 mg/m^2	Every 2 weeks	Giantonio et al. 2007(49)	IV
	Irinotecan	150 mg/m^2	Every 2 weeks		IV
Capecitabine	Capecitabine	2,500 mg/m^2	Daily for 2 week, followed by 1 week off	Capecitabine SmPC 2022(102)	Oral

Abbreviations: CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil and irinotecan; IV, intravenous; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; VEGF, vascular endothelial growth factor.

Table 75 Acquisition cost per administration

Regimen	Treatment	Dose per administration (mg)	Dose RDI (%)	Cost per administration
Primary treatments				
TAS-102	Trifluridine/tipiracil	63	89%	£102.17
Pooled FOLFOL/FOLFIRI	Folinic acid	720	100%	£28.38
	Oxaliplatin	153	100%	£183.98
	Fluorouracil	1800	100%	£31.10
Paclitaxel	Paclitaxel	144	100%	£287.93
Doxorubicin	Doxorubicin	108	100%	£80.73
Paclitaxel	Paclitaxel	136	100%	£271.93
FOLFIRI	Irinotecan	680	100%	£4,071.97
	Folinic acid	680	100%	£26.80
	Fluorouracil	4080	100%	£70.50
Nab-paclitaxel	Folinic acid	720	100%	£28.38
	Oxaliplatin	153	100%	£183.98
	Fluorouracil	1800	100%	£31.10
mFOLFOX	Oxaliplatin	180	100%	£216.45
	Fluorouracil	4320	100%	£74.65
	Folinic acid	180	100%	£7.10
mFOLFIRI	Irinotecan	270	100%	£1,616.81
	Folinic acid	180	100%	£7.10
	Fluorouracil	4320	100%	£74.65
Subsequent treatments				
Regorafenib	Regorafenib	160	91%	£178.29
Anti-VEGF + chemotherapy	Bevacizumab	700	100%	£1.79
	Folinic acid	720	100%	£28.38
	Oxaliplatin	153	100%	£183.98
	Fluorouracil	1800	100%	£31.10
Anti-EGFR + chemotherapy	Panitumumab	420	100%	£1,593.02
	Irinotecan	324	100%	£1,940.17
	Folinic acid	720	100%	£28.38
	Fluorouracil	5580	100%	£96.42
FOLFIRI	Irinotecan	324	100%	£1,940.17
	Folinic acid	720	100%	£28.38
	Fluorouracil	5580	100%	£96.42
Irinotecan	Irinotecan	306	100%	£1,832.39
Ramucirumab + paclitaxel	Ramucirumab	569	100%	£0.89
	Paclitaxel	144	100%	£287.93
Gemcitabine + paclitaxel	Gemcitabine	2250	100%	£347.90
	paclitaxel	270	100%	£539.87
Megestrol	Megestrol	288	100%	£1.17
FOLFOX	Folinic acid	720	100%	£28.38
	Oxaliplatin	153	100%	£183.98
	Fluorouracil	360	100%	£14.19
Fulvestrant	Fulvestrant	500	100%	£80.03
Tamoxifen	Tamoxifen	20	100%	£0.11
Fluorouracil + irinotecan	Fluorouracil	4320	100%	£74.65
	Irinotecan	270	100%	£1,616.81

Regimen	Treatment	Dose per administration (mg)	Dose RDI (%)	Cost per administration
Capecitabine	Capecitabine	4500	100%	£2.94
Abbreviations: EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil and irinotecan; IV, intravenous; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin; VEGF, vascular endothelial growth factor.				

B.3.5.1.1.3 Administration costs

The costs of treatment administration are sourced from NHS reference costs 2020-2021(103) and PSSRU 2021(104) costs are detailed in Table 76.

Table 76 Drug administration costs

Method	Cost	Source
Prescription	£0.00	Assumption
IV - simple - first attendance	£361.53	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance, Total HRGs
IV - complex - first attendance	£427.80	SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance, Total HRGs
IV - subsequent	£470.62	SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle, Total HRGs
Oral chemotherapy	£245.23	Deliver Exclusively Oral Chemotherapy SB11Z, Total HRGs
Fulvestrant - loading	£229.43	1st administration: NHS Reference Costs 2020/21 - CL WF01B, Medical Oncology (£355.28) + 2nd administration: NHS Reference Costs 2020/21 - CL WF01A, Medical Oncology (£224.55; outpatient assumed to be 33.3%) + PSSRU Table 10.1 Band 5, Curtis & Barnes, 2021 (£44.00; primary care assumed to be 66.7% Divided by 2 to reflect that the loading dose is administered twice in the first cycle: (355.28 + [224.55 * 0.33 + 44.00 * 0.67]) / 2 = £229.43
Fulvestrant - maintenance	£103.58	NHS Reference Costs 2020/21 - CL WF01A, Medical Oncology (224.55; outpatient assumed to be 33.3%) + £103.58
Abbreviations: IV, intravenous.		

B.3.5.2 Subsequent therapy costs

Following progression on pembrolizumab or on any of the comparator therapies included in the model, patients may receive further rounds of active therapy. In the base case, it was assumed that the same proportion of patients, regardless of initial line of therapy, would receive subsequent treatment. Although the model allows for a

unique percentage of patients transitioning to subsequent therapy after progression from each treatment regimen dependent on tumour site, it was assumed that the same proportion of patients regardless of initial line of therapy, would receive subsequent treatment. Data to inform these measures was based on the proportion of patients receiving one or more subsequent therapies in KN-164 and KN-158.(38, 41) 26.64%, 22.89%, 19.61%, 40.74% and 33.33% of patients in the CRC, endometrial, gastric, small intestine and cholangiocarcinoma tumour sites, respectively, were assumed to receive subsequent therapy after progression. Costs were applied as a one-off cost upon transition out of the PFS state.

Duration of subsequent therapy was derived from KN-164 and KN-158 data.(38, 41) Each subsequent treatment regimen is associated with a unique median time on treatment input; however, for simplicity an average was used based on the available data. As such, it was assumed that all subsequent regimens in the CRC, endometrial, gastric, small intestine and cholangiocarcinoma tumour sites would be associated with [redacted] and [redacted] days on subsequent treatment, respectively.

The treatment distribution of subsequent therapies is reported in Table 77, based on subsequent treatment distributions in KN-158 and KN-164. Each subsequent therapy regimen is associated with the same dosing, drug acquisition cost, administration, and RDI, as in the initial line of therapy reported in Table 74 and Table 75, where applicable.

Table 77 Subsequent therapy distribution

Tumour site	Subsequent therapy distribution						
CRC	**Regorafenib**	**Anti-VEGF + chemotherapy**	**TAS-102**	**Anti-EGFR + chemotherapy**	**FOLFOX**	**FOLFIRI**	**Fluoropyrimidine monotherapy**
	9.68%	35.48%	6.45%	16.13%	6.45%	19.35%	6.45%
Endometrial	**Doxorubicin**	**Paclitaxel**	**Megestrol**	**Fulvestrant**	**Tamoxifen**		
	20.00%	20.00%	20.00%	20.00%	20.00%		
Gastric	**FOLFIRI**	**Irinotecan**	**Paclitaxel**	**Ramucirumab + paclitaxel**			
	20.00%	20.00%	20.00%	40.00%			
Small intestine	**Gemcitabine + paclitaxel**	**Ramucirumab + paclitaxel**	**FOLFOX**	**FOLFIRI**			
	20.00%	20.00%	20.00%	40.00%			
Cholangiocarcinoma	**Capecitabine**	**Fluorouracil + irinotecan**	**FOLFOX**				
	50.00%	25.00%	25.00%				

Abbreviations: CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil and irinotecan; IV, intravenous; FOLFOX, folinic acid, fluorouracil and oxaliplatin; VEGF, vascular endothelial growth factor.

B.3.5.3 Health-state unit costs and resource use

Healthcare resource use (HCRU) in the cost-effectiveness analysis were sourced from previous NICE technology appraisals in relevant indications.

Costs for HCRU applied in the model were sourced from the NHS Schedule of Reference Costs, and the PSSRU. Where unit costs could not be identified, costs published in the relevant NICE technology appraisals were inflated using the PSSRU inflation index. HCRU frequencies were multiplied by unit costs to generate a per-cycle HCRU cost for each treatment in the progression-free and PD health states separately.

Detailed HCRU and costs are presented in Appendix K. The calculated weekly HCRU costs by health state are presented by tumour site in Table 78, and applied to all treatments in each tumour site per cycle.

Table 78 Health care resource use – cost summary

Tumour site	HCRU costs by health state (per cycle)	
	Progression free	**Progressed disease**
CRC	£2.75	£54.00
Endometrial	£73.75	£44.75
Gastric	£211.30	£18.71
Small intestine	£211.30	£18.71
Cholangiocarcinoma	£31.12	£57.16
Abbreviations: CRC, colorectal cancer; HCRU, health care resource use		

B.3.5.4 Adverse reaction unit costs and resource use

The costs applied for each AE are included in Appendix K. AE unit costs were taken from NHS Reference Costs and PSSRU costs where possible(103, 104); if not, then relevant literature sources were used. Costs for each AE are described in Appendix K. Where no relevant code could be identified, values were taken from published literature and previous NICE technology appraisals.

The cost of managing Grade 3+ AEs was applied as a one-off cost for patients entering the model (see Table 79).

Table 79 Summary of adverse reaction costs by tumour site

Treatment	Tumour site				
	CRC	Endometrial	Gastric	Small intestine	Cholangiocarcinoma
Pembrolizumab	£59.59	£213.59	£230.83	£151.97	£47.71
Comparator 1	£844.47	£640.30	£527.29	£218.70	£433.19
Comparator 2	£140.76	£640.30	£1,142.40	NA	£557.16

Abbreviations: CRC, colorectal cancer.

Notes: Comparator 1 = CRC, TAS-102; endometrial, paclitaxel; gastric, paclitaxel; small intestine, nab-paclitaxel; cholangiocarcinoma, mFOLFOX.
Comparator 2 = CRC, pooled FOLFOX/FOLFIRI; endometrial, doxorubicin; gastric, FOLFIRI; small intestine, NA; cholangiocarcinoma, mFOLFIRI.

B.3.5.5 Miscellaneous unit costs and resource use

B.3.5.5.1 Testing costs

Section B.1.3 describes testing guidelines recommended by NICE, as well as the precedents set for MSI-H patients in previous appraisals. In the model base case, testing costs are not included; the inclusion of these is explored in scenario analyses (Section B.3.11.3.

In the scenario analysis, testing costs to identify MSI-H/dMMR patients are applied in the first model cycle to patients in the pembrolizumab treatment arm. Cost inputs for PCR and IHC tests are presented in Table 80. Testing costs are also accrued for patients who test negative for MSI-H/dMMR tumours and are therefore not eligible for pembrolizumab treatment (i.e. proportion needed to test are also costed). The proportion of patients receiving each test and the proportion of those patients who test positive (see Table 81) is therefore used to calculate the costs of testing in the pembrolizumab arm for each tumour site (Table 82). The proportions of patients who are tested in current clinical practice, for each tumour site, are based on assumptions informed by UK clinical experts (Table 81).(1) As testing in CRC and endometrial is well established in the NHS, costs for these sites are never not included (this is also consistent with recent appraisals). Clinicians were unsure of a UK proportion tested for the remaining sites, so it was assumed that 50% would already be receiving tests, as a compromise. Testing costs for pembrolizumab per tumour site (Table 82) are calculated as the proportion of patients receiving each test multiplied by the respective test unit costs.

Table 80 Unit costs of tests for MSI-H/dMMR tumours

	Unit cost	Cost year	Model cost	Source
Costs of PCR testing for MSI-H	£202.00	2015/16	£224.20	NICE DG27(105)
Costs of IHC testing for dMMR	£210.00	2015/16	£233.08	NICE DG27(105)
Costs of IHC and PCR testing for both MSI-H and dMMR	-	-	£457.27	Calculation

Abbreviations: dMMR, DNA mismatch repair deficient; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; PCR, polymerase chain reaction.
Notes: Costs inflated to 2020/21 prices using the PSSRU inflation indices.

Table 81 Testing in current clinical practice

	CRC	Endometrial	Gastric	Small intestine	Cholangiocarcinoma
Proportion of patients already receiving MSI-H/dMMR testing in current clinical practice	100%	100%	50%	50%	50%
Proportion of patients receiving PCR testing for MSI-H (only)	15%	10%	10%	15%	15%
Proportion of patients receiving IHC testing for dMMR (only)	75%	70%	60%	75%	75%
Proportion of patients receiving both PCR and IHC testing for MSI-H/dMMR	10%	20%	5%	10%	10%
Proportion of patients who test positive for MSI-H/dMMR	4%(106)	17%(7)	9%(7)	8%(7)	3%(7)
Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficient; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; PCR, polymerase chain reaction.					

Table 82 Testing costs by tumour site

Tumour site	CRC	Endometrial	Gastric	Small intestine	Cholangiocarcinoma
Testing costs for pembrolizumab	£0.00	£0.00	£1,028	£1,589	£4,236
Abbreviations: CRC, colorectal cancer					

B.3.5.5.2 End-of-life costs

A one-off cost is applied in the model to reflect the cost of end-of-life care. The sources of end-of-life costs were selected based on previous NICE technology appraisals in each tumour site. A summary of the costs and sources used is presented in Table 83. Costs from each source were inflated using the PSSRU inflation index and then applied upon patient death in the model.

Table 83 shows the model base case end-of-life costs for each tumour site. CRC, gastric and cholangiocarcinoma tumour sites were taken from Round et al. (2015) (107), which is a standard source used for palliative and hospice care costs in submissions to NICE; in particular, this source was used to inform end-of-life costs in TA716 (CRC), TA669 (gastric cancer) and TA772 (biliary cancer).(65, 108)2015(107), which is a standard source used for palliative and hospice care costs in submissions to NICE; in particular, this source was used to inform end-of-life costs in TA716 (CRC), TA669 (gastric cancer) and TA772 (biliary cancer).(65, 108)

For endometrial, end-of-life costs were sourced from a study of healthcare utilization and hospital expenditures for patients in the final 30 days of life in the US. This cost was estimated to be $10,384 in Thurgar et al. (2021) and was applied in the model at the point of death. The cost was then converted from USD to GBP using an exchange rate of 0.82.(109)

For the small intestine tumour site, a study by Abel et al. (2013) was used, based on a cohort of hospice patients in South West England.(110) Costs were provided for death in hospital (£11,299, n = 108) and death elsewhere (£7,730, n = 556) and weighted to give an average cost of £8,737. This was inflated and used to inform end-of-life costs in TA488 (small intestine).

Table 83 End-of-life costs

Tumour site	Cost	Cost year	Model cost	Source
Colorectal	£6,343.00	2013/14	£7,197.50	Round et al. 2015(107)
Endometrial	£8,971.11	2018/19	£8,971.11	Thurgar et al. 2021(109)
Gastric	£6,343.00	2013/14	£7,197.50	Round et al. 2015(107)
Small intestine	£11,299.00	2011/12	£11,299.00	Abel et al. 2013(110)

Cholangiocarcinoma	£6,343.00	2013/14	£7,197.50	Round et al. 2015(107)
Notes: costs inflated to 2020/21 prices using the PSSRU inflation indices.				

B.3.6 Severity

Patients with previously treated MSI-H/dMMR solid tumours experience a profound worsening in both their expected length of life and their quality of life (Section B.1.3.1). The QALY shortfall calculator developed by Schneider et al. (2022) was used to generate absolute and proportional QALY shortfall estimates using the reference case HRQL norms (HSE 2017-18 EQ-5D-5L mapped to EQ-5D-3L using the Hernandez Alava et al. algorithm).(111, 112) Patient characteristics used in the analysis were consistent with those informing the base-case economic analysis (Table 84).

Table 84 Summary features of QALY shortfall analysis

Factor	**Value (reference to appropriate table or figure in submission)**					**Reference to section in submission**
Tumour site	CRC	Endometrial	Gastric	Small intestine	Cholangiocarcinoma	
Distribution* (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.2
Proportion male (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.1
Starting age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Section B.3.3.1
Abbreviations: CRC, colorectal cancer; QALY, quality-adjusted life year. **Notes:** * The proportion of patients in the overall population presenting with cancer in each tumour site						

Pembrolizumab is the first therapy evaluated for the treatment of patients with MSI-H/dMMR solid tumours across multiple tumour sites. Therefore, there are no previous economic evaluations to provide alternative QALY shortfall estimates. Within individual tumour sites, for the majority of comparator treatments it was not possible to calculate QALY shortfall based on data reported in previous appraisals as total QALY estimates were redacted (CRC, TA405; endometrial, TA779, ID3811; gastric, TA378; cholangiocarcinoma, TA722).(30, 31, 65, 113, 114) Where possible, QALY shortfall estimates based on results of relevant prior appraisals have been

provided in Table 85. General population QALY estimates were derived using the patient characteristics considered in this economic evaluation (Table 84), with total QALYs for current treatments sourced from the relevant appraisal.

Table 85 Summary list of QALY shortfall from previous evaluations

TA	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
TA716, FOLFIRI, CRC	[redacted]	[redacted]	[redacted]	[redacted]
TA716, FOLFIRI, CRC	[redacted]	[redacted]	[redacted]	[redacted]
TA378, docetaxel, gastric	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid, fluorouracil and irinotecan; QALY, quality-adjusted life year.
Source: TA716; Table 11, ERG base case results. TA378, Table 3.

To calculate estimates of total QALYs expected with current treatment, health state utilities consistent with those used in the base case were applied. This included utility values reported by progression status for CRC and utility values reported by time to death for all other tumour sites based on data collected from KN-158.(70) QALY shortfall calculations therefore assume that utility values for patients treated with 'current treatment' are informed by data collected from patients treated with pembrolizumab in all tumour sites except CRC – for CRC they are sourced from a study of patients treated with regorafenib.(67) Therefore, the resulting QALY shortfall estimates provided in Table 86 are likely to drastically underestimate the true severity of the condition given that utility values used in the current analysis are expected to overestimate the quality of life of patients treated with existing treatments. In addition, severity may be further underestimated given that many of the sources for comparator efficacy are not MSI-H/dMMR selected (e.g., sources for CRC comparators) and so survival and accrued QALYs may be overestimated. This is particularly relevant to CRC given how close the proportional shortfall is to the 95% boundary.

Table 86 Summary of QALY shortfall analysis

Tumour site	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
CRC	13.58	[redacted]	[redacted]	[redacted]	1.2
Endometrial	11.32	[redacted]	[redacted]	[redacted]	1.2
Gastric	10.40	[redacted]	[redacted]	[redacted]	1.7
Small intestine	12.96	[redacted]	[redacted]	[redacted]	1.7
Cholangiocarcinoma	12.35	[redacted]	[redacted]	[redacted]	1.7
Abbreviations: CRC, colorectal cancer; QALY, quality-adjusted life year.					

The updated NICE manual and corresponding materials suggest that the committee adopt a suitable approach with respect to the QALY shortfall analysis based on the requirements of each appraisal.(66, 115) The approach used in this evaluation was to estimate QALY shortfall estimates for each tumour site, based on the weighted SoC used in the economic analysis and associated QALY norms for the general population. This approach accounts for differences in the expected shortfall for individual tumour sites. For the gastric, small intestine and cholangiocarcinoma tumour sites, this resulted in a 1.7x QALY modifier weight. For the colorectal and endometrial tumour sites, the QALY shortfall resulted in a 1.2x QALY modifier weight. Weighted cost-effectiveness results for the overall indication presented in Section B.3.10 include these tumour-site-specific QALY weights.

The results of the QALY shortfall analysis are unsurprising given that virtually all previous appraisals in these second-line-plus settings received QALY weights consistent with the original end-of-life criteria: TA405 and TA716 in CRC, TA779 in endometrial cancer, TA722 in biliary cancer, ongoing ID1465 in gastric cancer, and, notably, the ongoing review of TA669 in gastric cancer that received a 1.7x QALY weight under the QALY shortfall analysis.

B.3.7 Uncertainty

Uncertainty in the available evidence base has been thoroughly explored where possible through evaluation of the associated parameter uncertainty and testing of the various structural assumptions made within the economic model. The key areas of uncertainty in the economic analysis are considered to be the following:

- Patients presenting with MSI-H/dMMR tumours are rare as a result of the low frequency of the mutation. Consequently, data collected for individual tumour sites are in some cases from a small number of patients

- The prognostic value of MSI-H/dMMR is uncertain but likely predicts worse survival outcomes for patients with metastatic cancer, which was validated by clinicians. In addition, clinicians were more certain about MSI-H/dMMR status being a positive treatment effect modifier for immunotherapies. Comparator survival outcomes are primarily collected from patients unselected for MSI-H/dMMR, which may bias relative efficacy estimates against pembrolizumab

- Reporting of baseline characteristics in most published studies is poor, making it impossible to adjust for imbalances in possible confounders

- OS data collected for patients treated with pembrolizumab are relatively mature. However, as a function of the profound improvement in survival outcomes achieved by treatment with pembrolizumab, a significant proportion of patients remain at risk at the end of the follow-up period, meaning that long-term survival outcomes remain uncertain

- Exploring and capturing heterogeneity in an economic analysis of treatment of tumours in multiple sites is associated with significant methodological challenges. The application of BHM methods to extrapolate time-to-event outcomes has been recommended in the academic literature but has not previously been used in the context of HTA. However, the assumption of complete heterogeneity of outcomes across tumour sites is reflected in the scenario analysis with individual parametric survival models

B.3.8 Managed access proposal

Should the Committee decide that they cannot recommend pembrolizumab in this population for routine commissioning (the Company's preference), the Company believes that this indication could be candidate for the CDF. Areas of uncertainty that could be addressed via additional data collection include (but are not limited to) the following:

- Subsequent KEYNOTE-158 data-cuts to test pembrolizumab OS and PFS model projections (e.g. under different methods such as BHM and curve selections)
- Subsequent KEYNOTE-158 data-cuts to obtain potentially more accurate data for utility analyses
- Real-world NHS pembrolizumab uptake proportions across tumour sites to validate weightings of MSI-H/dMMR tumour sites used in the blended SoC comparator

B.3.9 Summary of base case analysis inputs and assumptions

B.3.9.1 Summary of base case analysis inputs

Base case results are presented for a UK publicly funded health care payer for pembrolizumab versus a blended SoC comparator weighted over the five tumour sites of interest. The weighting for tumour sites was based on the clinical trial proportions in KN-158 and KN-164. QALY weighting was applied directly to the accrued QALY outcomes.

Table 87 gives the base-case settings used in the cost-effectiveness model. A summary of the variables is reported in Appendix J2.

Table 87 Base-case settings

Setting	Base-case setting	Reference to Section in submission
Perspective	UK publicly funded health care payer	Section B.3.2
Time horizon	40 years	Section B.3.2.2.1
Source of patient characteristics	KN164 and KN-158	Section B.3.2.1

Setting	Base-case setting	Reference to Section in submission
Source of tumour site distribution	KN-158/ KN-164	Section B.3.3.2
Source of efficacy data for pembrolizumab	KN-158/ KN-164	Section B.3.3.3.1 and Section B.3.3.5.1
Source of utility values	KN-158	Section B.3.4.1
Source of subsequent treatments	KN-158/ KN-164	Section B.3.5.2
Age/gender utility adjustment	Yes	Section B.3.4.5
Treatment waning	Yes	Section B.3.3.9

B.3.9.2 Assumptions

The main assumptions in the economic model alongside supporting justification are presented in Table 88.

Table 88 Assumptions and justification of the economic model

Base-case assumptions	Justification
General settings	
Population	Patient characteristics based on KN-158/ KN-164, which was agreed to be representative of UK clinical practice by clinical experts.(1)
Tumour site prevalence	KN-158/KN-164 trial based
Time horizon	40 years (lifetime)
Discount rate	Costs and QALYs at an annual discount rate 3.5% based on NICE reference case
Costs	
Drug costs	The cost of pembrolizumab (inclusive of confidential PAS) is reflected in presented results. TAS-102 has a confidential PAS in place, but the results reflect the list price.
Drug wastage	No wastage assumed. Relative dose intensities included where available based on clinical practice.
Stopping rules	Stopping rule applied for pembrolizumab. No other relevant stopping rules.
Subsequent therapies	Proportion of patients receiving subsequent therapy and mean time on treatment informed by KN-158/KN-164.
Testing costs	Not included, based on clinical expert opinion.(1)
EoL care costs	Included, applied as a one-off cost upon death.
Utilities	
Utilities values	TTD utility values informed by KN-158. TTD utilities preferred by clinical experts, who noted that TTD is more plausible for immunotherapy treatments(1) Health state utility values informed by Grothey et al. 2013.
AE costs	Included, applied as one-off upon health state entry.
AE disutilities	Not applied in the base case to avoid double counting.

Base-case assumptions	Justification
Survival and time of treatment extrapolations	
Intervention OS	Log-normal BHM
Intervention PFS	Log-normal BHM
Intervention TTD	All KM data complete. Data applied directly.
Comparator OS	Standard PSMs – see base case distributions.
Comparator PFS	Standard PSMs – see base case distributions.
Comparator TTD	Assumed equivalent to PFS (HR vs PFS = 1) for treatments when recommended by clinical experts.(1) For the remaining treatments, an exponential distribution was fitted to the reported median time on treatment estimate.
Treatment effect waning	Treatment effect waning applied to all patients between 7 and 9 years from treatment initiation. Approach is considered to be a highly conservative upper end.(1)
General population utility and mortality	OS and PFS hazards adjusted to ensure they exceed general population hazard of death at all times. Utilities adjusted for age-related decline accounting for the gender distribution within each tumour site.(88)
Abbreviations: AE, adverse event; BHM, Bayesian hierarchical model; EoL, end of life; HR, hazard ration; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TA, technology assessment; TTD, time to treatment discontinuation.	

B.3.10 Base case results

B.3.10.1 Base case incremental cost-effectiveness analysis results

Table 89 displays base case cost-effectiveness results for the overall indication (i.e. applied as the average results across tumour sites, weighted by tumour site prevalence). The histology-specific cost-effectiveness results are presented in Table 90. All presented cost-effectiveness analysis results reflect the confidential pembrolizumab PAS. The only known comparator with a PAS is TAS-102 (Trifluridine/ Tipiracil), although this comparator PAS is not reflected in results below.

Time-preference discounting, as described in Section B.3.2.2.1, is applied to all cost and QALY outcomes shown, but not life year estimates, unless otherwise stated. All results reflect a QALY weight of 1.2 for the CRC and endometrial sites and 1.7 for gastric, small intestine, cholangiocarcinoma as described in Section B.3.6 applied to the incremental QALY gains.

When weighted across all tumour sites, pembrolizumab is estimated to offer an additional [redacted] discounted QALYs versus SoC. High per-patient incremental health benefits are also estimated when considering the tumour sites individually, with

incremental QALYs above [redacted] in all sites. The estimated deterministic ICER for pembrolizumab, in all instances, is lower than a willingness-to-pay threshold of £30,000. The net health benefit (NHB), in all instances, is positive, signifying that health would be increased as result of the intervention, net of any additional costs associated with adoption of pembrolizumab (i.e., indicates cost-effectiveness).

Table 89 Base case results: overall indication

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB
SoC	£33,758.60	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,796	1.85

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.

Table 90 Base case results: histology specific

Tumour site	Total costs (£)		Total QALYs		Incremental outcomes			
	Pembrolizumab	SoC	Pembrolizumab	SoC	Δ Costs (£)	Δ QALYs	ICER (£)	NHB
CRC	[redacted]	£44,237.61	[redacted]	[redacted]	[redacted]	[redacted]	£8,754	1.92
Endometrial	[redacted]	£24,352.13	[redacted]	[redacted]	[redacted]	[redacted]	£15,014	1.78
Gastric	[redacted]	£28,106.03	[redacted]	[redacted]	[redacted]	[redacted]	£15,695	1.39
Small intestine	[redacted]	£34,793.15	[redacted]	[redacted]	[redacted]	[redacted]	£15,054	2.51
Cholangiocarcinoma	[redacted]	£22,017.09	[redacted]	[redacted]	[redacted]	[redacted]	£12,350	2.02

Abbreviations: CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

The cost-effectiveness model allows the user to generate probabilistic results for any of the programmed settings options, including all scenario analyses reported in Section B.3.11.3. Probabilistic sensitivity analysis (PSA) results for the base case analysis are summarized in tabular format across Table 91 for the overall indication and Table 92 by tumour site, inclusive of modifier QALY multipliers. These results show that the mean PSA ICER is highly congruent to the deterministic base case ICER (in Table 89 and Table 90). The PSA results shown are based on 1,000 random draws from input parameter distributions; the mean PSA ICER appears robust to additional PSA draws, as illustrated by the convergence plot within the cost-effectiveness model and Appendix J2.

The cost-effectiveness acceptability curve is displayed in Figure 43 to demonstrate the probability of pembrolizumab being cost-effective versus SoC at increasing willingness-to-pay thresholds. The analysis indicates that, when adjusting for severity-of-disease modifiers, pembrolizumab is cost-effective in 100% of probabilistic iterations. The cost-effectiveness plane is presented in Figure 44. This plots the mean incremental costs and QALYs of the PSA, alongside the deterministic incremental costs and QALYs to highlight the effect of parametric uncertainty in the analysis. This demonstrates that every PSA iteration estimates offers an incremental QALY benefit for pembrolizumab versus SoC at a positive incremental cost.

Figures by each individual tumour site and comparator are provided in Appendix J.

Table 91 Mean PSA results – overall indication

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB (QALYs)
SoC	£34,116.98	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,637	1.90

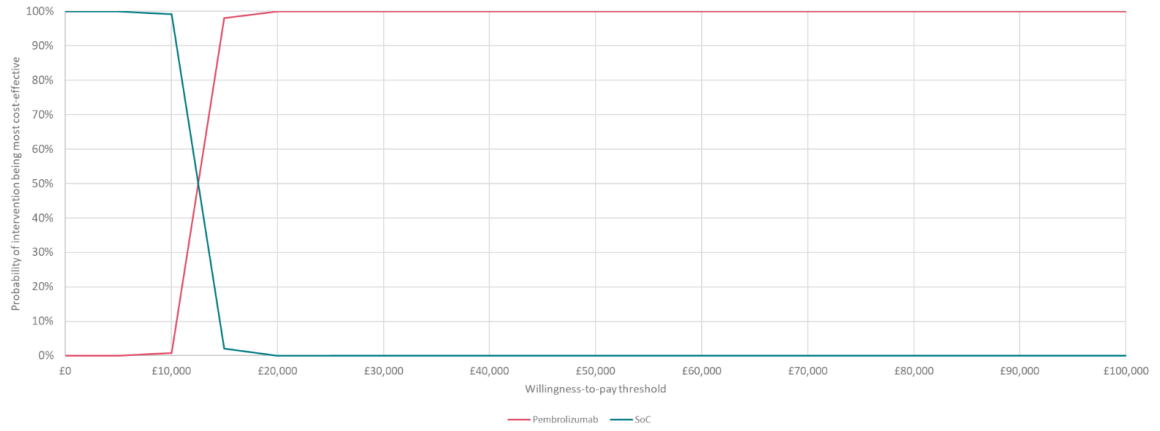
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SoC, standard of care.

Table 92 Mean PSA results – histology specific

Tumour site	Total costs		Total QALYs		Incremental outcomes			
	Pembrolizumab	SoC	Pembrolizumab	SoC	Δ Costs	Δ QALYs	ICER	NHB
CRC	[redacted]	£44,213.53	[redacted]	xxx	[redacted]	[redacted]	£8,813	1.91
Endometrial	[redacted]	£25,127.86	[redacted]	xxx	[redacted]	[redacted]	£14,826	1.80
Gastric	[redacted]	£28,923.90	[redacted]	xxx	[redacted]	[redacted]	£14,729	1.63
Small intestine	[redacted]	£35,064.97	[redacted]	xxx	[redacted]	[redacted]	£15,140	2.49
Cholangiocarcinoma	[redacted]	£22,002.10	[redacted]	xxx	[redacted]	[redacted]	£12,196	2.05

Abbreviations: CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; SoC, standard of care.

Figure 43 PSA Cost-effectiveness acceptability curve: overall indication, pembrolizumab vs SoC



Abbreviations: PSA, probabilistic sensitivity analysis; SoC, standard of care.

Figure 44 PSA Cost-effectiveness plane: overall indication, pembrolizumab vs SoC

[redacted]

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care.

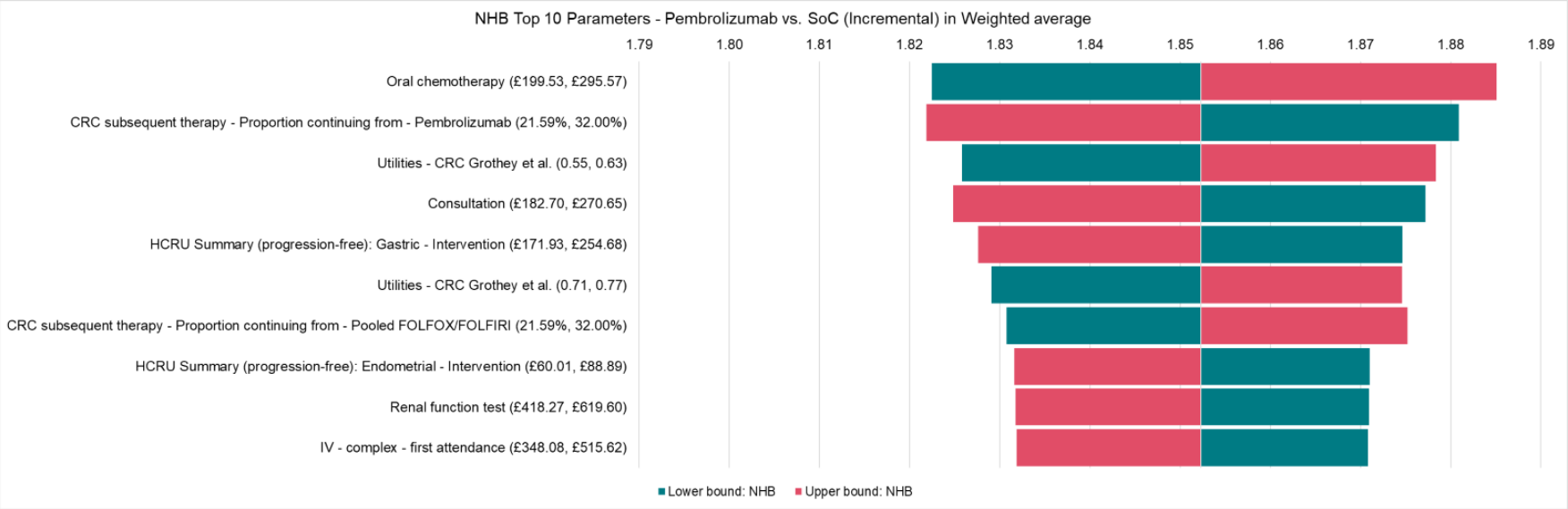
B.3.11.2 Deterministic sensitivity analysis

Figure 45 shows a tornado diagram depicting the 10 parameters that have the greatest influence on the NHB versus SoC in one-way sensitivity analyses (OWSA) for the overall indication. Tornado diagrams by tumour site are provided in Appendix J2.

For the OWSA, values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the CIs reported in Appendix J2. In this analysis, NHB results were most sensitive to parameter uncertainty around the cost of a medical oncology consultation (assumed to be a required medical resource for multiple tumour sites) and the utility value sourced from Grothey et al. (2012) for the CRC tumour site.

When interpreting the results of the OWSA, it should be noted that only parameters that could be varied in isolation were included. For correlated parameters, such as survival parameters and utility regressions, a multivariate normal distribution (using variance covariance matrices) was used in the PSA to capture uncertainty whilst maintaining the correlation between parameters; exploring the upper and lower limits within OWSA is not appropriate for such parameters. In addition, most parameters only impact a single tumour site, so while they may be impactful in a particular site, they may well be less impactful on the overall results when compared to any parameter that affects multiple sites.

Figure 45 Tornado diagram showing OWSA NHB results – overall indication pembrolizumab vs SoC



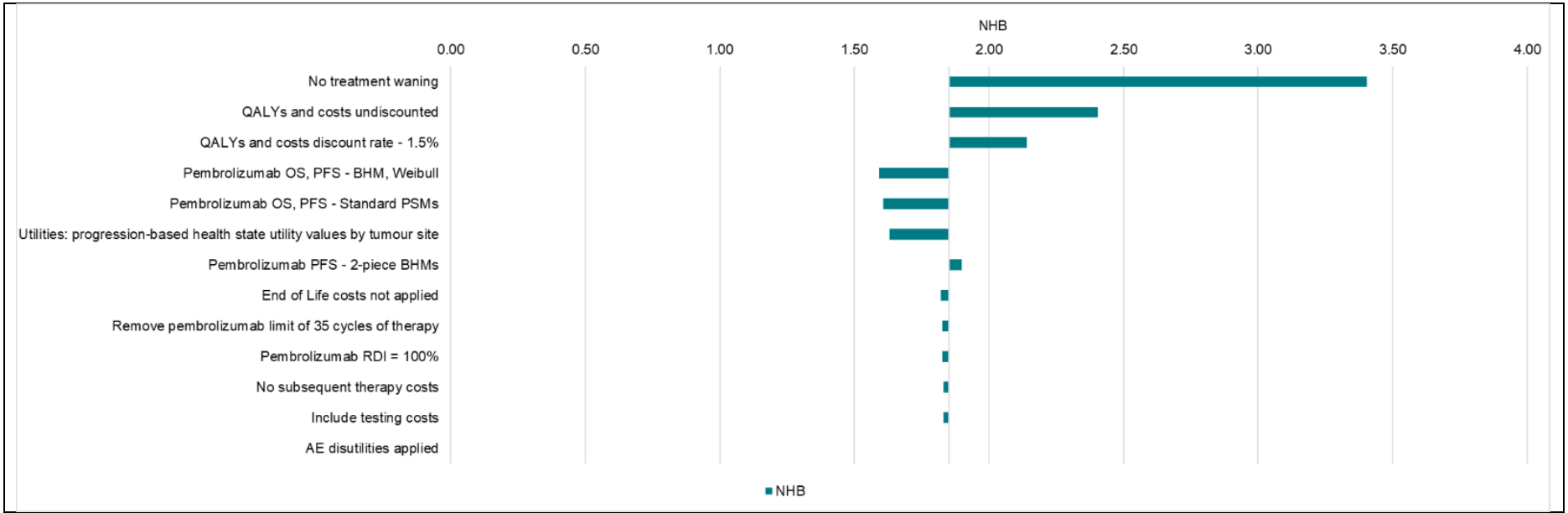
Abbreviations: CRC, colorectal cancer; HCRU, health care resource use; NHB, net health benefit; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care

B.3.11.3 Scenario analysis

The scenario analyses reported here test the sensitivity of cost-effectiveness results to structural uncertainties in the cost-effectiveness analysis. Figure 46 shows a tornado diagram depicting the influence of each scenario of interest on the NHB versus SoC. This is also presented in Table 93.

Summary results are generally robust to changes tested across the broad range of scenarios. The most impactful scenarios are those associated with removal of treatment effect waning and annual time-preference discount rate assumptions.

Figure 46 Tornado diagram showing scenario analysis NHB results: overall indication pembrolizumab vs SoC



Abbreviations: AE, adverse event; BHM, Bayesian hierarchical model; CRC, colorectal cancer; HCRU, health care resource use; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; SoC, standard of care.

Table 93 Scenario analysis NHB results: overall indication pembrolizumab vs SoC

Rank	Scenario	Incremental Costs	Incremental QALYs	NHB	Difference from Base Case
1	No treatment waning	[redacted]	[redacted]	3.40	1.55
2	QALYs and costs undiscounted	[redacted]	[redacted]	2.40	0.55
3	QALYs and costs discount rate - 1.5%	[redacted]	[redacted]	2.14	0.29
4	Pembrolizumab OS, PFS - BHM, Weibull	[redacted]	[redacted]	1.59	-0.26

5	Utilities: progression-based health state utility values by tumour site	[redacted]	[redacted]	1.61	-0.24
6	Pembrolizumab OS, PFS - Standard PSMs	[redacted]	[redacted]	1.63	-0.22
7	Pembrolizumab PFS - 2-piece BHMs	[redacted]	[redacted]	1.90	0.05
8	End of Life costs not applied	[redacted]	[redacted]	1.82	-0.03
9	Remove pembrolizumab limit of 35 cycles of therapy	[redacted]	[redacted]	1.83	-0.03
10	Pembrolizumab RDI = 100%	[redacted]	[redacted]	1.83	-0.03
11	No subsequent therapy costs	[redacted]	[redacted]	1.83	-0.02
12	Include testing costs	[redacted]	[redacted]	1.83	-0.02
13	AE disutilities applied	[redacted]	[redacted]	1.85	0.00

Due to the programming of the economic model, to allow weighting of results across tumour sites, it was not possible to automate scenario analyses exploring different tumour site prevalence rates. Results are generated separately and are reported in Table 94.

Table 94 Tumour site prevalence scenario using UK epidemiological data

Technologies	Incremental costs (£)	Incremental QALYs	ICER	Difference from base case	NHB	Difference from base case
SoC	-	-				
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.

B.3.12 Subgroup analysis

Not applicable.

B.3.13 Benefits not captured in the QALY calculation

The use of pembrolizumab may result in potential substantial HRQL benefits for patients' caregivers which have not been explicitly captured in the QALY calculation. It has been demonstrated that for patients with cancer, their cancer and its associated treatment can be associated with a significant HRQL impact on their caregivers and families. In addition, as one of the tumour sites included in this indication is that of endometrial tumours, there are likely to be additional quality-of-life impacts for people with wombs who are of child-bearing age with such tumours, as well as on their partners/families that may not be captured in the QALY calculation.

As the indication to be appraised is in tumours where previous treatments have failed and where the disease may be progressing rapidly, the speed of progression of the cancer can make collection of nuanced quality-of-life and health-utility data in these patients challenging, both practically and ethically.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Substantial efforts have been undertaken to validate the modelling approach and results. This section describes, in turn:

- Expert opinion used to guide the modelling approach
- Quality checks performed on the model
- Comparison with other trial data, including extrapolation of OS, median OS and PFS estimates, and OS at key time points (1 and 2 years).

B.3.14.1.1 Expert opinion

Expert clinical and health economic input was sought during the development of the cost-effectiveness model. This helped to ensure that the inputs and assumptions used in the base case analysis were relevant to UK clinical practice in order to validate the clinical plausibility of the outcomes predicted by the model. An advisory board of clinical experts was conducted whereby model inputs and assumptions were discussed and validated.(1) Six clinicians with experience across each of the tumour sites and one health economist attended the advisory board. Topics covered in the advisory board included:

- Unmet medical need in patients with MSI-H tumours;
- The current clinical pathways and comparator landscape in UK practice;
- The use of MSI-H/dMMR as a prognostic factor;
- Access to testing for MSI-H tumours;
- Tumour site prevalence;
- Comparator market shares;
- Estimating relative efficacy of pembrolizumab, the use of Bayesian hierarchical modelling, and survival curve extrapolations;
- Quality of life estimates;
- Subsequent therapies.

B.3.14.1.2 Model functionality checks

Internal validity checks were conducted by an independent modeller to test the model mechanics and technical functionalities. A quality control (QC) check was conducted using the internal checklist developed using publicly available checklists such as Drummond and Philips as a guide.(116, 117) The checklist also includes all checks listed in the published TechVER checklist.(118) The formal internal QC is in addition to regular checks and reviews that are performed by the modelling team

throughout the model development. The formal QC was led by an experienced, unconflicted health economist who had not been involved in the development of the original model.

Separately, statistical analyses were subject to rigorous validation of programming. For example, the results of the BHM analyses were validated through double programming and visual inspection of the diagnostic, marginal posterior distributions, and model predictions.

B.3.14.1.3 Comparison to other trial data

Model outcomes were also validated against relevant NICE appraisals and literature identified in the SLR and TLRs (Appendices G, H, and I).

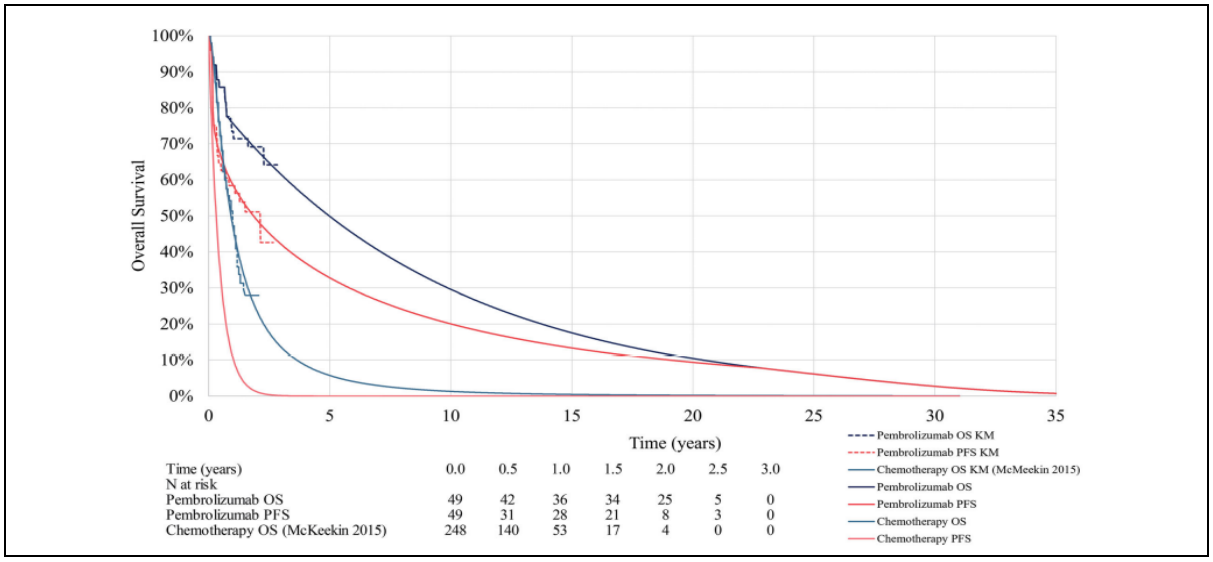
B.3.14.1.3.1 Validation of survival inputs

Given the confidentiality of survival data in previous NICE TAs, survival curves from the cost-effectiveness model were validated against relevant literature, in addition to clinical validation (described in Section B.3.14.1.1).

Thurgar et al. (2021) reported survival data in the US for women with previously treated MSI-H/dMMR unresectable or metastatic endometrial cancer (Figure 47).(109) For OS, there is close alignment between 0 and 15 years in Thurgar et al. (2021) compared with the observed values in the endometrial tumour site within the cost-effectiveness model, for both pembrolizumab- and chemotherapy-treated patients. For progression-free survival, values in Thurgar et al. (2021) are greater than those estimated in the cost-effectiveness analysis. In addition, a study by Bellone et al.(2022) evaluated a small cohort of patients with MSI-H endometrial cancer; outcomes are uncertain given the small patient numbers but suggest KN-158 provides a conservative estimate of survival outcomes for MSI-H endometrial cancer. (119)

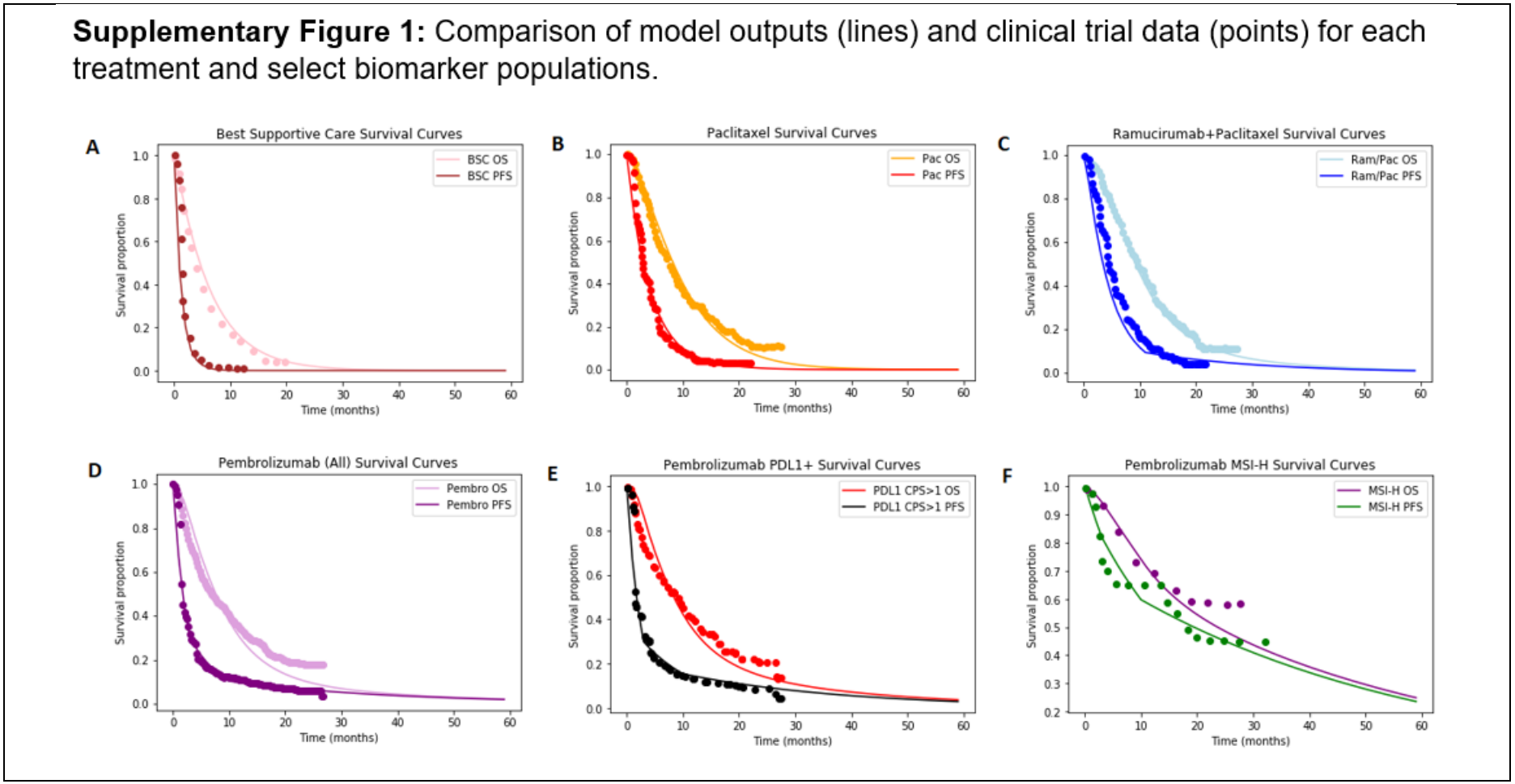
Lauren et al. (2020) demonstrated survival in second-line metastatic gastric cancer. For patients with MSI-H disease treated with pembrolizumab (Figure 48; Panel F), again, survival estimates support those predicted in the cost-effectiveness model.

Figure 47 Survival data from Thurgar et al. (2021)



Abbreviations: KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

Figure 48 Survival data from Lauren et al. (2020)



Abbreviations: BSC, best supportive care; CPS, combined positive score; MSI-H, microsatellite instability-high; OS, overall survival; PFS, progression-free survival.

B.3.14.1.3.2 Validation of results

Given the difference in modelling assumptions between the cost-effectiveness model and relevant studies identified in the SLR, specific comparisons are limited. Generally, comparator LYs and QALYs results in the cost-effectiveness analysis are within a reasonable range in the base case compared to the studies identified in the SLR for CRC, gastric cancer, and cholangiocarcinoma. This is also the case for pembrolizumab in endometrial and small intestine carcinoma studies. Base case results of economic modelling studies identified in the SLR are presented in Appendix G.

B.3.15 Interpretation and conclusions of economic evidence

The economic SLR and subsequent TLR updates identified no previous economic evaluations of treatments for patients with MSI-H/dMMR solid tumours in multiple tumour sites (Appendix G). Therefore, a de novo economic model was developed to support this submission. The economic analysis drew relevant inputs from previous appraisals of therapies for tumour sites included in the approved indication.

The economic evaluation compares health outcomes for patients treated with pembrolizumab with those of patients treated with relevant comparators identified by UK clinical experts, for each of the included tumour sites. The comparator is modelled as a blended SoC comparator reflective of the variation in treatment selection seen in current clinical practice. Results are presented separately by tumour site as well as for the overall approved indication.

The economic evaluation builds on approaches used in previous appraisals of therapies indicated for multiple tumour sites(72, 73) while applying novel methodology in the form of Bayesian hierarchical models in order to satisfy the recommendations of NICE to explicitly explore and capture heterogeneity.(66, 74) BHMs are used to capture heterogeneity of survival outcomes between tumour sites for patients treated with pembrolizumab. Heterogeneity related to other clinical and cost outcomes was also captured through the use of appropriate tumour-site-specific sources. Whilst this is a complex decision problem, every effort has been made to

follow new NICE recommendations and to incorporate learnings from the previous submissions for histology-independent therapies.

Cost-effectiveness results evaluated deterministically and probabilistically demonstrate pembrolizumab to be a highly cost-effective intervention, both within each tumour site and across the whole approved indication. Patients benefit from significantly improved survival outcomes, as well as reduced HRQL decrements due to the superior safety profile of pembrolizumab compared with that of often highly toxic comparator chemotherapy regimens. Improved health outcomes are associated with greater costs for patients treated with pembrolizumab, largely as a function of higher drug acquisition costs as well as an increase in HCRU costs due to patients surviving longer.

Parameter and structural uncertainty were explored through PSA, univariate OWSA and scenario analysis. Overall, the sensitivity and scenario analyses explored indicate that, under a range of assumptions, pembrolizumab is associated with a positive NHB corresponding to an ICER below the NICE willingness-to-pay threshold adjusted for the severity-of-disease decision modifier. Cost-effectiveness results were shown to be most sensitive to removing treatment effect waning, implementing a shorter time horizon and a higher discount rate. In particular, the treatment effect waning explored in the base case is considered an upper end extreme and clinically implausible worst-case scenario, whereby from 7 to 9 years after treatment initiation, patients treated with pembrolizumab experience no durable treatment effect and assumes the survival probabilities associated with the comparator therapy. In most cases, nearly all patients treated with currently available treatments have died by 7 years, leading to implausible scenarios where the probability of survival immediately drops to 0. Despite this extreme stress testing, the NHB of pembrolizumab was still high at 1.91, corresponding to an ICER of £12,224.

Other scenarios – including conservative survival extrapolations for pembrolizumab, changes in subsequent therapy, end-of-life costs, health-state utility approach and use of an alternative tumour site prevalence source – all resulted in small reductions in NHB. In addition, the impact of using standard parametric survival models to

extrapolate pembrolizumab OS and PFS (in contrast to the BHM), fitted independently by tumour site, only marginally increased the ICER.

Several key assumptions within the economic evaluation are considered conservative or likely to bias against pembrolizumab. The majority of comparator studies were conducted in patients unselected for MSI-H/dMMR. Published evidence suggests MSI-H/dMMR is prognostic of worse survival outcomes in metastatic cancer (and almost certainly a treatment effect modifier), so not adjusting for this likely underestimates the relative effectiveness of pembrolizumab.(22) In addition, the model assumes for all tumour sites that health state utilities are equivalent for patients treated with pembrolizumab or comparator therapies. This likely overestimates the HRQL of patients receiving treatments as part of the existing standard of care comprised of often toxic multi-component chemotherapy regimens compared to the targeted immunomodulatory profile of pembrolizumab.

The key strength of the current economic evaluation is the transparent and flexible framework within which it harnesses the latest available pivotal trial data from KN-158 and KN-164 and best available comparative data from published sources. The evaluation applies methods consistent with the relevant NICE DSU TSD recommendations and is consistent with the NICE reference case and the relevant decision problem. Results of the economic evaluation presented here indicate pembrolizumab is a highly cost-effective treatment option for patients with previously treated MSI-H/dMMR solid tumours and that this conclusion is robust and consistent, as shown by a comprehensive range of sensitivity and scenario analyses.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Summary of Information for Patients (SIP)

February 2023

File name	Version	Contains confidential information	Date
NICE ID4036 – pembrolizumab previously treated solid tumours dMMR MSI-H - SIP	1.1	No	08 February 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Pembrolizumab (KEYTRUDA®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population being appraised by NICE is adult patients that have certain types of cancers that are at an advanced stage. Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. These cells may form tumours, which are lumps of tissue (1). Patients that are eligible for this treatment must be diagnosed with cancer of any of the following sites of the body: • Colon or rectum • Endometrium • Stomach • Small intestine • Biliary tract Patients must also be diagnosed with cancer at an advanced stage. Early-stage cancers may be curable through treatments such as surgical resection, where the tumour is removed. When a cancer is diagnosed at an advanced stage this can mean that the cancer has spread beyond one organ and it cannot be removed entirely by surgery (2). Patients must also have their tumours tested to determine the 'microsatellite instability' or 'mismatch repair' status (fully detailed in section 2) and be found to be microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR). Patients must also have had a prior therapy for treating their cancer.

The exact wording of the patient population being appraised by NICE is below:

Adults with unresectable or metastatic MSI-H or dMMR colorectal cancer previously treated with fluoropyrimidine-based combination therapy.

Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation.

Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Regulatory approval for pembrolizumab in the indication relevant to this appraisal was granted for Great Britain by the Medicines and Healthcare products Regulatory Agency, the MHRA: (PL GB 53095/0040) on 16 May 2022 (3).

The indication relevant to this appraisal is provided below:

Pembrolizumab (KEYTRUDA) as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

- *treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.*

Pembrolizumab (KEYTRUDA) as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- *advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;*
- *unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.*

Pembrolizumab has already been approved by the MHRA for the first-line treatment of adults with MSI-H or dMMR colorectal cancer (3). In addition, pembrolizumab, as monotherapy or in combination with other agents, is licenced for specific indications in:

- Melanoma
- Non-small cell lung cancer
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Oesophageal cancer
- Triple-negative breast cancer (TNBC)
- Endometrial carcinoma
- Cervical cancer

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The table below shows you MSD's involvement with the patient groups that are listed as stakeholders for this appraisal.

Stakeholder	Financial transaction in 2022	Have met with MSD	Relationship
Cancer 52	£10,000	Yes	MSD is a corporate supporter of Cancer52. Our support runs from December 2022-December 2023.
Genetic Alliance UK	No	Yes	We have met with Genetic Alliance once in 2022 to discuss corporate membership.
Go Girls	No	Yes	We have sought insights from Go Girls to understand the patient pathway and lived patient experience with endometrial cancer.
Guts UK	No	Not within last 6 months	Guts UK provided a quote for inclusion in a SMC press release in Q1 2022.
Macmillan Cancer Support	No	Yes	Macmillan Cancer Support are a partner of our "Do It For Yourself", lung cancer signs and symptoms campaign. https://www.msd-uk.com/wp-content/uploads/sites/43/2022/02/Do-It-For-Yourself-Campaign-Evaluation-Report-Jan-2022.pdf
Peaches Womb Cancer Trust	No	Yes	We met with Peaches ahead of a Scottish Medicines Consortium (SMC) and NICE appraisal to understand the patient journey and experience of endometrial cancer. Peaches Womb Cancer Trust provided a quote for inclusion in a press release following SMC approval.
Tenovus Cancer Care	No	Yes	MSD are a corporate member of Wales Cancer Industry Forum' which Tenovus are a leading partner.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

As described in section 1b, patients eligible for this indication of pembrolizumab have certain types of advanced MSI-H or dMMR cancers.

General signs and symptoms of advanced cancer can include:

- Loss of energy and feeling tired and/or weak: This can get so bad that you may have a hard time doing everyday tasks like bathing or getting dressed. People with advanced cancer often need help with these activities.
- Weight loss (without trying)
- Pain
- Shortness of breath or trouble breathing

Advanced and metastatic cancers can cause many other symptoms, depending on the type of cancer and where it has spread (4).

Though these cancers can occur in adults of any age, the likelihood of someone getting diagnosed with these cancers increase with age, and that likelihood increases more so from age 50. With the exception of endometrial cancer, the majority of the population diagnosed are male. The age and sex of patients diagnosed is given in the table below. The peak rate of diagnosis refers to the age range a patient is most likely to be diagnosed with that cancer.

	Peak rate of diagnosis in the UK	**Proportion of females diagnosed in England**
CRC (5)	85-89	44%
Endometrial Cancer (6)	75-79	100%
Gastric Cancer (7)	85-89	35%
Small Intestine Cancer (8)	80-84	45%
Biliary Cancer	Data not available	Data not available

Every patient's journey with cancer is different. However advanced cancer patients face a very short life expectancy of typically less than one year after their diagnosis. (9) The survival data specific for each tumour in the licence are presented in the table below, where the percentages describe the proportion of all patients that survived that timeframe after being diagnosed with stage IV cancer. Stage IV refers to a cancer that has spread to at least one other body organ (10).

	1-year survival (%)	3-year survival (%)	5-year survival (%)
CRC	43.7	16.4	10.3
Endometrial Cancer	46.9	19.6	11.5
Gastric Cancer	23.2	5.3	3.8
Small Intestine Cancer	No data available	No data available	No data available
Biliary Cancer	No data available	No data available	No data available

Source: (9)

The table below describes how many adults were diagnosed with each of these five cancers in England in 2020, at any stage and at the advanced stages.

	Incidence (all stages)	Incidence for patients with stage 3 and 4 at diagnosis (all ages)
Colorectal Cancer	34,396	16,835
Endometrial Cancer	7,567	1,380 (ICD10 code: C54 to C55)
Gastric Cancer	5,053	No data available by stage
Small Intestine Cancer	1,690	No data available by stage
Biliary Cancer	3,200	No data available by stage

Source: (11)

As also previously described, patients must also have their tumours tested for MSI-H/dMMR. MSI is microsatellite instability. A microsatellite is a short sequence of DNA. DNA contains genetic information. The sequence is repeated in each of your cells. The DNA in the cell stays the same in each repeat. If an error occurs, a normal gene is able to correct it. Sometimes a normal gene develops changes or mutations. It is no longer able to correct errors in the DNA. This makes the DNA, and the whole microsatellite, unstable. A cancer cell with a high level of MSI is described as "MSI high" (12). Mismatch repair deficiency (dMMR) refers to a lack of certain genes that are involved in correcting mistakes made when DNA is copied in a cell (13). If a tumour is found to be MSI-H it is likely to be a result of mismatch repair deficiency.

The proportion of people with MSI-H tumours (the prevalence of MSI-H) varies by where the tumour is. Several tumour sites, including endometrial, colorectal, and gastric cancers were consistently found to have the highest MSI-H prevalence, generally above 5% (14). For most other cancers, MSI-H prevalence was below 5% (15). The prevalence of MSI-H at Stage IV is given in the table below.

	Proportion of stage IV patients with MSI-H tumours (16)
Colorectal Cancer	4-8%
Endometrial Cancer	6-11%
Gastric Cancer	5-8%
Small Intestine Cancer	2-6%
Biliary Cancer	1-3%

MSI-H and dMMR can be associated with Lynch Syndrome, a condition in which higher risk of these and other cancers is passed down through families (17).

NICE recommends testing cancers for MSI to identify patients that may have Lynch syndrome. If Lynch syndrome is diagnosed, treatment and surveillance can be offered to reduce the risk of having another Lynch syndrome-associated cancer or to identify it earlier. Testing for Lynch syndrome can also be offered to relatives with the aim of preventing Lynch syndrome-associated cancer developing or detecting as early as possible (18, 19).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Some people start by seeing their GP if they have symptoms that could be due to cancer. After examination the GP may make a referral to a specialist. Some people are diagnosed with cancer after they become unwell and go to accident and emergency (A&E). The latter is more common for patients who are diagnosed with advanced cancers.

Various tests are required to diagnose cancer, dependant on the site of the tumour. If cancer is confirmed more tests will be conducted to find out how big it is and to stage the disease (20).

Once a patient is diagnosed with either CRC or endometrial cancer, NICE recommends further testing to identify MSI-H/dMMR, and identify Lynch syndrome (18, 19). NHS England also already pays for MSI-H testing for gastric, small bowel and biliary cancers. (21).

A test for MSI-H will show the level of instability in the DNA of the cancer cells. The test compares normal tissue to tumour tissue for differences in size. A positive MSI-H test means that the tumour is very unstable. Doctors have found that certain immunotherapy drugs may work well

against MSI-H tumours in some patients. This is because the immune system may be able to find and attack cancer cells with high MSI more easily (13).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

When a cancer reaches an advanced stage treatment options that aim to cure are no longer possible. Cancers that have spread beyond one organ may be most suitable for a "systemic" therapy, referring to a drug therapy that works throughout the whole body (22). Though very unlikely to provide a cure, systemic therapies can improve a patient's quality of life and prolong life.

Two common types of systemic therapy are chemotherapy and immunotherapy. Chemotherapy attacks all rapidly-dividing cells within the body, effectively targeting fast-growing tumours. Immunotherapy helps the immune system do a better job of identifying cancer cells so it can attack and kill them (23).

Before immunotherapy, chemotherapies were widely recommended for these five cancers in treatment guidelines across the UK, Europe and the United States. (24-28)

There is some research that suggests that chemotherapy works less well for patients with advanced cancer who test positive for MSI-H or dMMR than patients who test negative (29-31). It has also been shown in a global study that some colorectal cancer patients who test positive for microsatellite instability may survive longer and have fewer serious side effects on immunotherapy vs chemotherapy (32). Only recently has there been enough data collected from studies into immunotherapy and patients with advanced MSI-H cancers to lead to the MHRA to approving immunotherapies (3, 33, 34) as a treatment for these patients and NICE to recommend them (32). (35) (36).

The NICE recommendations for MSI-H/dMMR patients that have had prior therapy are listed in the table below. Please note that dostarlimab is currently only recommended within the cancer drugs fund (a time limited source of funding), and due for further review in April 2025 (37).

Colorectal tumours	Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA716) (35) Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405) (38)

Endometrial tumours	Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency (TA779) (36)

Through this appraisal MSD are aiming to seek a NICE recommendation for pembrolizumab for the patients following prior therapy who are still otherwise limited to chemotherapy. It is hoped through a successful appraisal, that more patients with MSI-H tumours will be given the opportunity to receive an immunotherapy.

The population in scope aims to address the unmet need of the relevant gastric, small bowel and biliary cancer patients. MSD also wish pembrolizumab to be appraised as a new treatment option in endometrial, given that dostarlimab is not yet recommended for baseline (a more permanent) funding. MSD also wish to be appraised as a treatment option in CRC where the current immunotherapy options may not be suitable.

To fully describe the desired positioning of pembrolizumab we first outline therapies we expect patients receive before pembrolizumab.

We expect patients with CRC receive a prior chemotherapy that contains fluoropyrimidine, such as Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) or Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) (39).

We expect endometrial cancer patients receive a chemotherapy that contains platinum, such as carboplatin.

For patients with gastric, small intestine or biliary cancer the prior therapies that are recommended are specific to the type of cancer, and are usually one chemotherapy used alone or a few used in combination concurrently.

Below we outline the therapies that are currently used after the above:

	Second Therapy
CRC	Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) Oxaliplatin plus leucovorin and 5-fluorouracil (FOLFOX-4) 5-Fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) Trifluridine-tipiracil
Endometrial	Paclitaxel Doxorubicin Carboplatin
Gastric	Paclitaxel FOLFIRI
Small Bowel	FOLFIRI FOLFOX
Biliary	FOLFIRI FOLFOX

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the

medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients with advanced cancers are faced with many challenges, including symptoms of tumour and its spread to other organs, the difficulties with taking chemotherapy, and the mental and emotional impacts associated with the diagnosis of a fatal illness.

Section 2a outlines the general symptoms of advanced cancers. Further symptoms are experienced based on the site of the cancer and where it has spread. For example, the general symptoms of advanced colorectal cancer include fatigue and suppressed appetite, however further symptoms may be felt based on if cancer has spread to the liver, lungs, or bones. If the cancer spreads to the liver, it can cause stomach pain and sickness. Spreading to the lungs can cause a long-lasting cough and breathlessness. Spreading to the bones can cause constipation and irritability. Cancer Research UK details the main symptoms associated with each cancer site and where it spreads (40).

Targeting the rapidly dividing cancer cells, chemotherapy aims to ease some of these symptoms. However further issues can be caused by the side effects of chemotherapy. Each person experiences side effects from chemotherapy differently, and different chemotherapy drugs cause different side effects (41). Many people feel fine for the first few hours following chemotherapy. Usually, some reaction occurs about four to six hours later. However, some people don't react until 12 or even 24 to 48 hours after treatment. Some people experience many side effects described, while others experience almost none. Some of the most common side effects are summarised below (42):

- Infection and fever – due to chemotherapy reducing a patient's white blood cell count, the cells that help fight infection, chemotherapy patients are more susceptible to infection. This can result in a fever.
- Flu-like symptoms - Around the third day following a chemotherapy treatment, some people may experience flu-like symptoms such as muscle aches and pains.
- Nausea (though not all chemotherapy drugs cause nausea).
- Fatigue, which can range from mild (usually cured by additional rest) to severe which may routinely impact a patient's ability to carry out everyday tasks such as cooking or bathing (43).
- Hair loss - begins about two to three weeks after starting chemotherapy. Some people will lose relatively little hair, while others may lose the hair on their head, eyelashes and eyebrows, as well as other body hair. Many people feel that hair loss is one of the most difficult aspects of chemotherapy treatment.

Beyond the impacts of the disease and treatment, advanced cancer patients must also deal several large life changes. Below we summarise a study into all the known research done into understanding these life transitions (44).

During change, people have to let go of familiar ways of living and redefine who they are. Other studies describe how patients and significant others experience transitions during the course of advanced cancer. For instance, patients say it feels like navigating through 'troubled water and landmines'. And, understanding that suffering from advanced cancer takes time, at first denial can

be felt by patients. Also, significant others feel transitions when caring for their loved one. For instance, when their loved one is taken to hospital, they experience both guilt and relief, because care and judgement is often handed over to hospital staff. Significant others also experience transitioning into feelings of helplessness and loneliness during the course of advanced cancer.

When reaching the point where cancer is advanced, patients use metaphors such as "getting a death sentence" and "losing their fight against cancer" to describe their situation.

Patients have multiple reactions when being given a diagnosis of advanced cancer, they need to connect with fellow travellers as they undergo a constant process of adaptation. Patients also experience the major change of being in a state of both living and dying. In this state, patients experience death moving closer, they try to make the best of what is left in life and they struggle with living in a sick body. As for significant others, they experience being in a constant process of both having and loosing. They struggle with entering and leaving caregiving, they have thoughts related to death and, throughout the course of the advanced cancer of their loved one, they need hope.

Living with advanced cancer involves a process of constant adaptation due to the changes caused by cancer. This experience is described as "opening one door after the other". Patients said they had feelings of uncertainty, unpredictability, powerlessness, living under constant pressure and changes. This results in patients living in at times indescribable and uncontrollable emotional chaos.

Patients experience changes within their body caused by cancer and cancer treatment. Their body becomes a threat; patients experience being prisoners in their own bodies; their body could not be trusted anymore; it becomes difficult to recognise their own body; the decay and deterioration of their body, for some patients, resulted in experiencing being afraid of themselves and being dependent on others.

Significant others take part in the dying process of their loved one during the course of advanced cancer. Death becomes impending and anticipated, but they strive to focus on living with a living person instead of a dying one. How significant others approach death varies, for instance by: thinking death is far off in the future; experiencing death moving closer when you talk about it; denying death - described with the metaphor: "Like the ostrich with my head in the sand". However, significant others prepare themselves for the death of their loved one by: facing that they are going to be left behind; talking about the facts of death; learning to face the fact that their loved one is going to die and having concerns of how to manage life afterwards.

During the course of advanced cancer, significant others also have experiences of hope. They describe the phenomena of hope as: a gradual, individual process, always changing and shifting; a struggle to maintain. Significant others hope for many things during their loved ones illness: improvement; a miracle; a cure and survival; prolonging of their loved ones life; illness phase to be over and finding balance; experiencing comfort; retaining everyday life - something potentially meaningful to look forward to. The presence of hope varies: significant others experience both living in hope, hopelessness and with low levels of hope during the course of illness - however, choosing hope allowed them to have some control of ups and downs and therefore, searching for new hope was a deliberate process; hope helped them to make sense of their completely changed situation; but hope could also be experienced as unrealistic.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

An important role of the immune system is the ability to differentiate between healthy and unhealthy cells. The level of activity of immune cells, such as T cells, is crucial to maintaining a balanced immune response.

Under normal conditions, a protein called programmed death-ligand 1 (PD-L1) which naturally occurs on cells, plays an important role in maintaining this balanced immune response. PD-L1 binds to its PD-1 receptor on immune T cells, which lessens the ability of immune T cells to attack. This ensures that normal cells are protected from excessive damage. However, PD-L1 is produced in larger amounts on cancerous cells than normal cells. As a result, when binding to PD-1 on immune T cells, this interaction tricks the immune system thereby protecting the tumour from being attacked by the body's immune system.

PD-1 inhibitors, such as pembrolizumab, act to block the checkpoint interaction between PD-1 and PD-L1 and by doing so, boost the immune response which helps the person's own immune cells to attack the cancer cells.

The summary of product characteristics (SPC) and the patient information leaflet (PIL) for pembrolizumab can be found by following this link:
https://products.mhra.gov.uk/search/?search=pembrolizumab&page=1

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Pembrolizumab is not intended to be used in combination with other medicines for this indication.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Pembrolizumab comes in a 25mg/mL concentrate solution for infusion. One 4mL vial of concentrate contains 100mg of pembrolizumab.

The recommended dose of pembrolizumab is 200mg administered by intravenous injection through an infusion into your vein (intravenous) over 30 minutes. Treatment will usually take place at an infusion clinic once every 3 weeks. Pembrolizumab can also be administered as a 400mg dose once every 6 weeks.

In line with its licence, pembrolizumab may be given for up to 35 cycles (approximately two years) as long as it is working (i.e. as long as the cancer does not progress) and side effects are tolerable. Scans are conducted regularly to keep track of response to treatment. Patients need to be monitored while on treatment for symptoms or side effects, and blood tests may be conducted to check for side effects (3).

The infusion time for pembrolizumab is shorter than the majority of the current chemotherapy regimens listed in section 2c, and a stark difference to the fluorouracil containing regimens that are typically administered over 46-48 hours (45).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

A search on clinicaltrials.gov for recruited, enrolling by invitation, active but not recruiting, or completed studies on pembrolizumab returns 1,570 (search conducted 13th Dec 22). 28 of these studies are in MSI-H cancers, and 18 of these studies have 100 or more patients, listed below. Further details of these studies can be found by searching for the study name on clinicaltrials.gov.

Study name	Phase	Location	Condition	n	Treatments studied	Expected completion date
NCT02563002	Phase 3	Global	Colorectal Carcinoma	307	Drug: mFOLFOX6|Drug: FOLFIRI|Biological: pembrolizumab|Biological: bevacizumab|Biological: cetuximab	May 15, 2023
NCT04895722	Phase 2	Global	Colorectal Cancer	320	Biological: Pembrolizumab|Biological: Pembrolizumab/Quavonlimab|Biological: Pembrolizumab/Favezelimab|Biological: Pembrolizumab/Vibostolimab|Biological: MK-4830	October 28, 2025
NCT05239741	Phase 3	China	Colorectal Neoplasms	100	Biological: Pembrolizumab|Drug: Oxaliplatin|Drug: Leucovorin|Drug: 5-fluorouracil|Drug: Irinotecan|Biological: Bevacizumab|Biological: Cetuximab	November 10, 2026
NCT05217446	Phase 2	Global	Metastatic Colorectal Cancer	104	Drug: Encorafenib|Biological: Cetuximab|Biological: Pembrolizumab	March 28, 2027
NCT02460198	Phase 2	Global	Colorectal Carcinoma	124	Biological: Pembrolizumab	February 19, 2021
NCT03374254	Phase 1	United States, Canada	Metastatic Colorectal Cancer	220	Biological: Pembrolizumab|Drug: Binimetinib|Drug: Oxaliplatin|Drug: Leucovorin|Drug: 5-Fluorouracil [5-FU]|Drug: Irinotecan	November 16, 2023
NCT02332668	Phase 1|Phase 2	Global	Melanoma|Lymphoma|Solid Tumor|Classical Hodgkin Lymphoma|Microsatellite-instability-high Solid Tumor	370	Biological: Pembrolizumab	May 6, 2025
NCT03836352	Phase 2	United States, Canada	Ovarian Cancer|Hepatocellular Carcinoma|Non-small Cell Lung Cancer|Bladder Cancer|Microsatellite Instability-High	184	Other: DPX-Survivac|Drug: Cyclophosphamide|Drug: Pembrolizumab	December 31, 2023
NCT04612309		Italy	Colorectal Cancer	100	Drug: Immunotherapy	June 30, 2023
NCT05572684	Phase 1|Phase 2	United States	Advanced or Metastatic Solid Tumors|Microsatellite Instability Low|Microsatellite Instability High|Microsatellite Stable|Ovarian Cancer|Gastric Cancer|Colo-rectal Cancer|Esophageal Cancer|Endometrial Cancer|Head Neck Cancer|Cervical Cancer|Lung Cancer	131	Drug: NC410|Drug: Pembrolizumab	01 November 2025
NCT04234113	Phase 1	United States, Czechia, France, Spain	Thyroid|Renal Cell Carcinoma|Non Small Cell Lung Cancer|Small-cell Lung Cancer|Bladder Cancer|Melanoma|Merkel Cell Carcinoma|Skin Squamous Cell Carcinoma|Microsatellite Instability High|Triple	200	Drug: SO-C101|Drug: pembrolizumab	01 December 2023

			Negative Breast Cancer|Mesothelioma|Thymic Cancer|Cervical Cancer|Biliary Tract Cancer|Hepatocellular Carcinoma|Ovarian Cancer|Gastric Cancer|Head and Neck Squamous Cell Carcinoma|Anal Cancer			
NCT05200559	Phase 1|Phase 2	United States	Epithelial Ovarian Cancer	70	Drug: Pembrolizumab|Drug: E7777	01 December 2027
NCT04244552	Phase 1	United States	Breast Cancer|Colorectal Cancer|Ovarian Cancer|Non-Small Cell Lung Cancer|Acral Lentiginous Melanoma|Head and Neck Squamous Cell Carcinoma|Hepatocellular Carcinoma|Esophageal Squamous Cell Carcinoma|Urothelial Carcinoma|DMMR Colorectal Cancer|MSI-H Colorectal Cancer|Melanoma|Platinum-Resistant Primary Peritoneal Carcinoma|Platinum-Resistant Fallopian Tube Carcinoma|Platinum-Resistant Epithelial Ovarian Cancer|Triple Negative Breast Cancer	240	Biological: ATRC-101|Biological: Pembrolizumab|Drug: Pegylated liposomal doxorubicin (PLD)	01 March 2025
NCT05098132	Phase 1	United States	Advanced Solid Tumor|Non Small Cell Lung Cancer|Head and Neck Squamous Cell Carcinoma|Malignant Melanoma|Renal Cell Carcinoma|Ovarian Cancer|Cervical Cancer|Microsatellite Instability High|Gastric Cancer|GastroEsophageal Cancer|Urothelial Carcinoma|Mismatch Repair Deficiency	202	Drug: STK-012|Drug: Pembrolizumab	01 October 2025
NCT04114136	Phase 2	United States	Melanoma|NSCLC|Hepatocellular Carcinoma|Urothelial Cancer|Gastric Adenocarcinoma|HNSCC|Esophageal Adenocarcinoma|Microsatellite Instability-High Solid Malignant Tumor	108	Drug: Nivolumab or Pembrolizumab (dependent upon approved indication)|Drug: Metformin|Drug: Rosiglitazone	01 December 2027
NCT03589339	Phase 1	United States	Radiotherapy|Immunotherapy|Microsatellite Instability-High Solid Malignant Tumour|Metastasis From Malignant Tumor of Liver|Squamous Cell Carcinoma of Head and Neck|Metastasis From Malignant Tumor of Cervix|Metastatic Renal Cell Carcinoma|Metastasis From Malignant Melanoma of Skin (Disorder)|Metastatic Triple-Negative Breast Carcinoma|Metastatic NSCLC|Metastasis From Malignant Tumor of Bladder (Disorder)	145	Drug: NBTXR3|Radiation: SABR|Drug: Nivolumab|Drug: Pembrolizumab	May 30, 2028
NCT02635672	Phase 1	United States, Chile	Neoplasms	110	Drug: VIP152 (BAY 1251152)|Drug: VIP152 (BAY 1251152) 30 mg|Drug: Keytruda|Drug: VIP152 (BAY 1251152) 15 mg	December 30, 2024
NCT03228667	Phase 2	United States	Non-Small Cell Lung Cancer|Small Cell Lung Cancer|Urothelial Carcinoma|Head and Neck Squamous Cell Carcinoma|Merkel Cell Carcinoma|Melanoma|Renal Cell Carcinoma|Gastric Cancer|Cervical Cancer|Hepatocellular Carcinoma|Microsatellite Instability|Mismatch Repair Deficiency|Colorectal Cancer	145	Drug: N-803 + Pembrolizumab|Drug: N-803 + Nivolumab|Drug: N-803 + Atezolizumab|Drug: N-803 + Avelumab|Drug: N-803 + Durvalumab|Drug: N-803 + Pembrolizumab + PD-L1 t-haNK|Drug: N-803 + Nivolumab + PD-L1 t-haNK|Drug: N-803 + Atezolizumab + PD-L1 t-haNK|Drug: N-803 + Avelumab + PD-L1 t-haNK|Drug: N-803 + Durvalumab + PD-L1 t-haNK	01 December 2023

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

There are two pembrolizumab clinical trials that were conducted that provide data for this appraisal: KEYNOTE-158 and KEYNOTE-164.

KEYNOTE-158 included patients with MSI-H/dMMR endometrial, gastric, small intestine and biliary tumours. KEYNOTE-164 included patients with MSI-H/dMMR colorectal tumours. Both studies included patients who had prior therapies, and were single-arm, phase 2, studies. This means that every patient on the study received pembrolizumab, and that there wasn't another group (or arm) on the current treatment to compare against (as you would expect in a phase 3 study). However, the cancers being considered in this appraisal are relatively rare and it would be difficult to recruit enough patients to run an additional phase 3 study that needs more patients to prove one treatment is better than another.

These studies set out to see how well pembrolizumab worked in patients with MSI-H/dMMR tumours in different organs of the body. To find this out the following key measures were taken:

1. **Objective response rate** – measured as a percentage, objective response rate, or ORR, is the proportion of patients in a trial whose tumour is destroyed or significantly reduced by a drug. ORR is generally defined as the sum of complete responses (CRs) – patients with no detectable evidence of a tumour over a specified time period – and partial responses (PRs) – patients with a decrease in tumour size over a specified time period. This is a useful measure for seeing how effective a drug is in shrinking a tumour.
2. **Progression-free survival –** typically measured in months or weeks, progression-free survival, or PFS, measures how long a person lives from the start of the trial without the disease worsening. PFS is considered an indication of disease control and stabilization. Taking the median, an average, PFS in a trial can be a useful measure of how long a patient may expect to live without the disease worsening after starting to take the medicine in the trial.
3. **Overall survival –** typically measured in months or weeks, overall survival, or OS, measures how long a person lives from the start of the trial until death. Taking the median, an average, OS in a trial can be a useful measure of how long a patient may expect to live after starting to take the medicine in the trial.

For each of the cancer sites these three measures are given in the table below. Please note that in addition to the values given, a range is also provided in brackets. This range refers to an upper and lower estimate between which you can be 95% certain the true value lies, (named 95% confidence interval, CI). NR refers to "Not Reached". This means that the studies have not yet been running for long enough for us to make a measurement.

	ORR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)
Colorectal	33.9 (25.6, 42.9)	4.0 (2.1, 7.4)	36.1 (24.0, NR)
Endometrial	50.6 (39.4, 61.8)	13.1 (4.9, 25.7)	NR (48.0, NR)
Gastric	37.3 (24.1, 51.9)	4.1 (2.1, 24.6)	26.9 (6.6, NR)
Small Intestine	55.6 (35.3, 74.5)	23.4 (4.3, NR)	NR (16.2, NR)

Biliary	40.9 (20.7, 63.6)	4.2 (2.1, 24.9)	19.4 (6.5, 44.8)

The data from this table was taken from KEYNOTE-164 at the 19-FEB-21 database cutoff date, and KEYNOTE-158 at the 15-OCT-21 database cutoff date.

Based on the measure definitions above, interpreting the Endometrial results for example, we may say:
This study found that approximately half (50.6%) of endometrial patients responded to pembrolizumab, resulting in a significant degree of tumour shrinkage. The median (average) patient remained free from worsening disease for about 13 months. We don't yet know how long the median (average) patient will survive after starting pembrolizumab in this trial, however using the lower confidence interval as a guide, there is a good chance that similar patients to those in this trial may expect to live more than 48 months.

A large part of this appraisal is to see whether pembrolizumab is a more effective treatment than current treatments. Since these trials did not collect any data on current treatments, then data from the clinical trials of the current treatments were collected for indirect comparison. Making comparisons in this way is difficult as there are often differences in the types of patients that take part in each trial. These differences may affect the result of the comparison. Even with this in mind, it does appear that the results of the pembrolizumab trials compare favourably vs the current treatments. More information is provided in the submission document B, section B2.9.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

No patient reported outcomes (PROs) or quality of life data was collected from KEYNOTE-164. For KEYNOTE-158 PROs used two types of questionnaire, the EORTC QLQ-C30, that looks specifically at the quality of life of cancer patients, and the EQ-5D, that looks at a the general health status of a patient (46).

The EQ-5D consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system has five questions on mobility, self-care, pain, usual activities, and psychological status with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem). Results from these questions can then be combined and scaled to produce a single score with a maximum score of 1. Scores can vary from 0, which represents death, to 1 which represents the best possible health state. The EORTC uses different questions, however also produces a score that is meant to represent a patient's quality of life. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. From this we can gather three scores (from the EQ-5D questionnaire, the EQ-5D VAD and the EORTC questionnaire) that can assess how a patient feels throughout their treatment.

Across all three methods, on average the patients reported a small improvement from starting the treatment to next questionnaire after 9 weeks of treatment. However, the scores were different depending on whether the patients achieved a response on pembrolizumab (i.e. their tumours

shrank by a significant amount). Patients who had a significant tumour shrinkage (a response) reported the largest improvement. Patients whose tumours neither grew nor shrank (stable disease) reported a smaller improvement. Patients whose tumours grew (progressive disease) reported a worsening score on the EQ-5D and EORTC questionnaires, and the smallest improvement on the EQ-5D VAD. Full details are available in the submission documents.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Pembrolizumab has been used in hospitals in England since 2015 (47). Section 1b describes the different cancers pembrolizumab has a licence in. The safety and side effects data from all the trials that have led to these licences are included in the pembrolizumab Summary of Product Characteristics (SmPC) (3). A summary of relevant safety information from the pembrolizumab SmPC has been provided below, giving doctors and other hospital staff clear guidance on what to do if a patient experiences an immune-related side effect.

The safety of pembrolizumab as monotherapy has been evaluated in 7,631 patients across tumour types. In this patient population, the median observation time was 8.5 months (range: 1 day to 39 months) and the most frequent adverse reactions with pembrolizumab were fatigue (31%), diarrhoea (22%), and nausea (20%). The majority of adverse reactions reported for monotherapy were of mild or moderate severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions. The incidences of immune-related adverse reactions were and 24.2% all Grades and 6.4% for Grades 3-5 in the metastatic setting.

Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones

The grading system for adverse reactions, or side effects, referred to above is explained in section 4a.

The side effects that were reported in the clinical trials KEYNOTE-158 and KEYNOTE-164 are consistent with the common side effects listed in the pembrolizumab SmPC. Below is a table of the most common side effects (occurring in more than 10% of patients) from patients relevant to this appraisal in KEYNOTE-158 and KEYNOTE-164. This table that was published in the European Public Assessment Report (EPAR), an evaluation of the evidence for this indication made on behalf of the European Medicines Agency (EMA). Please note that the below tables include any adverse effects (side effects) experienced whilst patients were on the clinical trial, including but not limited to the side effects caused by pembrolizumab. "n" refers to the number of patients in the trial and "%" refers to the proportion.

	KN158 Cohort K + KN164 Cohorts A and B MSI-H Data for Pembrolizumab‡‡	
	n	(%)
Subjects in population	475	
with one or more adverse events	455	(95.8)
with no adverse events	20	(4.2)
Diarrhoea	122	(25.7)
Fatigue	116	(24.4)
Nausea	106	(22.3)
Arthralgia	90	(18.9)
Vomiting	89	(18.7)
Asthenia	84	(17.7)
Pruritus	82	(17.3)
Abdominal pain	79	(16.6)
Anaemia	74	(15.6)
Constipation	72	(15.2)
Pyrexia	70	(14.7)
Decreased appetite	69	(14.5)
Back pain	63	(13.3)
Cough	59	(12.4)
Dyspnoea	57	(12.0)
Alanine aminotransferase increased	53	(11.2)
Hypothyroidism	53	(11.2)
Rash	52	(10.9)
Headache	49	(10.3)
Urinary tract infection	48	(10.1)

As described in section 3e there were no comparisons made vs standard treatment in KEYNOTE-158 or KEYNOTE-164. However, there are other clinical trials that have studied pembrolizumab vs chemotherapy, perhaps the most relevant to this population being KEYNOTE-177 which compared patients on pembrolizumab vs patients on standard of care chemotherapy for patients with untreated MSI-H/dMMR CRC. This study found there were more serious side effects for patients

on the chemotherapy, but more immune-mediated or infusion reaction side effects for patients on pembrolizumab (48).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits to patients, caregivers and communities may include:

- Some patients' tumours may shrink: As described in sections 3e and 3f, the studies found more than a third of patients in each of the tumour sites evaluated in this appraisal may find their tumours shrinking. The results from the patient reported outcomes suggests this may result some increase in quality of life.
- Though not certain, pembrolizumab may improve a patients' life expectancy vs chemotherapy. Caution must be taken as the studies described in section 3e did not compare pembrolizumab against chemotherapy.
- The average patient may have fewer serious side effects on pembrolizumab vs chemotherapy. As described in section 3e and 3g the studies did not compare against chemotherapy, however a different study has shown that patients on pembrolizumab have fewer serious side effects than patients on chemotherapy (48).
- The infusion time of pembrolizumab is short compared to some of the common currently used chemotherapies (i.e. fluorouracil), and pembrolizumab can be given every 6 weeks. This could result in shorter and less frequent visits to a hospital for patients.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The key disadvantages to patients, caregivers and communities may include:

- Some patients will need to make more journeys into hospital (or alternative site of care) to receive their infusions versus if they were on chemotherapy. The maximum treatment duration for pembrolizumab (2 years) is longer than chemotherapy regimens which typically last between 3 to 6 months (49). Provided that patients are getting on well with pembrolizumab then they could find themselves needing to make more journeys to receive more infusions.
- Patients are at an increased risk of developing immune related side effects, some of which may last beyond the patient stopping pembrolizumab (3). Please note there is clear guidance provided in the SmPC that instructs healthcare providers on how to manage these side effects.

- Pembrolizumab, like any other medicine, does not work the same in every patient. Not all patients' tumours shrink and it may not result in an extended life expectancy.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness relates to how much new health (or quality-adjusted life years, QALYs) the new medicine produces compared to its additional cost (vs. current care), for a typical/average patient and whether the new health is worth the extra cost.

The cost-effectiveness of pembrolizumab in this indication (vs. chemotherapies that patients would otherwise receive) is evaluated for the typical/average patient via modelling that uses short-term trial data to extrapolate efficacy and costs over a lifetime horizon.

The challenges of modelling average lifetime outcomes (overall survival, progression and quality of life) from trial data arise from the short-term nature of trials (KN-158 and KN-164 have around 5 years of patient survival data), the limited sample size for each tumour site and from the two trials being single arm so that patients only receive pembrolizumab (i.e. the trial does not have a comparator arm).

The cost-effectiveness model is used often in oncology and produces lifetime outcomes by tracking a typical/average patient cohort as they move through 3 health states - progression free, progressed and death – and averaging everything at the end to produce results for the typical/average patient receiving pembrolizumab (or the comparator chemotherapies) in this indication.

How long patients stay in each health state depends on the data from the two trials (Kaplan Meier curves for overall and progression-free survival). For the period beyond the trial, data extrapolation methods are used ("parametric survival models") and there is always uncertainty about which extrapolated curve fits the trial data the best and which curve estimate more plausible outcomes in the long term. Given that the trials contained no comparator arm, survival data for these were obtained from the literature (e.g., previous results from trials that roughly match the indication).

There will also be debates about whether additional adjustments should be made to pembrolizumab survival extrapolations that make the risks of progression or death closer to the

comparator treatments (what is called “treatment effect waning”). In this appraisal, this is less relevant because the observed survival data for pembrolizumab extends well beyond the time at which patients stop receiving pembrolizumab treatment (survival data has been collected for 5 years and patients receive the medicine for around 2 years) and most patients on comparator chemotherapies will have died after the observed trial period of 5 years.

A unique characteristic of this appraisal is the basket nature of the trial evidence: data on 4 of the 5 tumour sites in this appraisal were collected from the KEYNOTE-158 trial. The standard methods for extrapolating survival outcomes are further complicated by assumptions about whether each tumour site should be treated independently or whether some borrowing of information should take place between tumour sites (e.g., gastric or endometrial) when extrapolating survival data. The modelling allows for different methods to be applied, which make different assumptions about this. In particular, hierarchical methods allow variation in outcomes between tumour sites to impact survival extrapolations for each tumour site (e.g., endometrial data can have some impact on a site with a smaller sample size such as small intestine).

Pembrolizumab works by both helping to prevent patients from progressing and keeping progressed patients alive for longer than if they were receiving chemotherapies. According to clinical experts, some patients on pembrolizumab are also considered to become “functionally cured” and this proportion is likely to be established for the group of patients that have not progressed for 5 years.

Quality of life tends to be better for patients in the progression-free survival state (i.e., who have not progressed) compared with the progressed state. Given the improved survival – better PFS and OS – the typical pembrolizumab patient will tend to have a better quality of life than a patient receiving chemotherapies. How the model applies quality-of-life “weights” to time spent in the progression-free and progressed states depends on the method chosen: one method applies fixed weights to each health state and the other focusses more on the time to death which may be more relevant to patients who receive an immunotherapy like pembrolizumab. Different side-effect profiles of treatments can also impact overall quality of life, but this is not a big driver of results compared with the time spent in health states and time spent alive.

Results of the economic analysis show that pembrolizumab is cost-effective at commonly used thresholds compared with all chemotherapies across every tumour site and overall when a weighted average across tumours sites is calculated. As mentioned above, a significant amount of scenario analyses that use different methods in different combinations are presented. Some make the results look better and some worse for pembrolizumab but results consistently show pembrolizumab to be cost-effective.

Survival and quality-of-life outcomes for patients on chemotherapies are so severe compared with the general population of a similar age, that a severity modifier is likely to apply for this condition, which changes the threshold NICE considers a medicine to be cost effective. In particular, analyses show that for the less common tumour sites (gastric, small bowel and biliary) the highest modifier category should apply. This means that the usual standard for assessing cost-effectiveness is less relevant and higher thresholds apply in this appraisal, making pembrolizumab even more cost-effective.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
As mentioned in section 2c, there is some evidence to suggest that patients with MSI-H tumours may fair worse on chemotherapies vs non- MSI-H tumours. Immunotherapy is already commonly used for some patients with some MSI-H tumours, however there are many patients whose options are limited to succession of chemotherapies and these patients have the greatest unmet need. Subject to this appraisal, more patients with MSI-H tumours will have access to an immunotherapy option. With more available options, doctors and patients may be able to make better treatment decisions based on the MSI-H test result.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues are anticipated.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
CTCAE grading In oncology clinical trials, the severity of adverse events are usually graded according to US National Cancer Institute's AE Severity Grading Scale - Common Terminology Criteria for Adverse Events (CTCAE) (50). CTCAE can also be used to grade the AE for non-oncology studies, but generally not appropriate for studies using healthy volunteers. • Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated • Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL • Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g. bathing, dressing or feeding). • Grade 4 Life-threatening consequences; urgent intervention indicated. • Grade 5 Death related to AE. **Further information on NICE and the role of patients:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Abdominal pain – Pain in your belly or tummy area.
Alanine aminotransferase increased - In general, high levels of alanine aminotransferase (ALT) may be a sign of liver damage.
Anaemia - A low red-blood count. Your blood does not have enough of the cells that carry oxygen (haemoglobin) to your body. Also called "tired blood" or "low iron".
Arthralgia - Pain in your joints.
Aspartate aminotransferase increased - In general, high levels of aspartate aminotransferase (AST) may be also be a sign of liver damage.
Asthenia - Asthenia, also known as weakness, is the feeling of body fatigue or tiredness.
Constipation - Constipation is generally described as having fewer than three bowel movements a week.
Decreased appetite - A decreased appetite occurs when you have a reduced desire to eat.
Diarrhoea - Loose, watery stools three or more times a day.
Dyspnoea - When you have trouble breathing.
Fatigue - tired, weak feeling of the whole body, feeling tired all over.
Hypothyroidism - When your thyroid makes too much thyroid hormone.
Nausea - When you have an upset stomach or feel like throwing up.
Pruritus - Pruritus is a medical term that means itching. It refers to a feeling or sensation on your skin that you want to scratch.
Pyrexia - A body temperature that is higher than normal. Also called fever.
Rash - An area of skin that is itchy or swollen.
Urinary tract infection - A common infection anywhere in the body's waste and excess water "drainage" system (urinary tract). This includes kidneys, ureter, bladder, and urethra. Also called a UTI.
Vomiting - To throw up

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Clarification questions

February 2023

File name	Version	Contains confidential information	Date
ID4036 pembrolizumab clarification question to PM for company MSD responses [ACIC]	**1.0**	**Yes**	**20 February 2023**

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.

Note on changes made to model submitted with these clarification questions

For modelling options introduced during clarification stage, scroll to the bottom of Model Controls sheet and see new Clarification section. Changes include:

- Addition of KN-158 Jan 2022 KMs and refitted standard PSMs (see response to A28)
- Addition of functionality to prevent patients being treated beyond progression (see response to B20)
    - Programmed into scenario analysis
- Incorporation of within KN-061 HRs (see response to A32)
    - Programmed into scenario analysis
- Addition of functionality to calculate RMST (see response to B22)

Section A: Clarification on effectiveness data

Literature searches

All Clinical Effectiveness searches (for all conditions)

A 1. D1.1.1 suggested that each systematic literature review (SLR) was conducted across the same list of resources. The search methods and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart both report a search of the ClinicalTrials.gov registry.

Please provide full details, including the search strategies or search terms used, date searched, and results for all conditions.

The search terms, dates, and number of hits retrieved for each tumour site are shown in the tables below.

Biliary cancer

Search term	Search date	Restrictions	Hits
Condition or disease: Biliary Adenocarcinoma Other terms: --	29 September 2022	Age (18+); Study type (interventional)	189
Condition or disease: Gall Bladder Carcinoma Other terms: --		Age (18+); Study type (interventional)	193
Condition or disease: Hepatic Cholangiocarcinoma Other terms: --		Age (18+); Study type (interventional)	38

Total			420
Duplicates			72
# to screen			348

Colorectal cancer

Search term	Search date	Restrictions	Hits
Condition or disease: Colorectal cancer	20 October 2022	Study with results	321

Endometrial cancer

Search term	Search date	Restrictions	Hits
Condition or disease: Endometrial cancer	31 August 2022	Study with results	115

Gastric cancer

Search term	Search date	Restriction	Hits
Condition or disease: Gastric cancer/neoplasm	30 November 2022	Study with results	179

Small intestine cancer

Search term	Search date	Restrictions	Hits
Condition or disease: Small intestine	15 November 2022	Study with results	78

A 2. Please explain the rationale behind limiting all clinical effectiveness searches to English language publications only and discuss potential limitations of that restriction.

Searches were limited to English language publications due to the extensive resources and time required for a search unrestricted by language, including access to medical translation services for multiple languages. English is the most widely used language for scientific communication and, as these systematic literature reviews (SLR) concern clinical trials of interventions approved for use in the UK, relevant studies, particularly in terms of population and setting, are likely to have been published in English. Furthermore, a recent systematic review suggests that restricting systematic reviews to English language results may have limited impact on conclusions (1).

Limitations of restricting the searches to English language publications are acknowledged. By imposing the language restriction, relevant publications published in languages other than English may not be identified. Additionally, this method may bias the results of the systematic review toward the perspectives of English-speaking countries and populations. Overall, restricting the search to English language publications allowed the SLRs to consider the most likely relevant information with the time and resources available.

A 3. Please confirm whether any additional searches were conducted to retrieve information regarding adverse events (AEs) for treatment of each condition, and, if yes, provide full details including date, resource names and search strategies used.

Separate searches specific to adverse events were not conducted. Adverse events were considered relevant outcomes for study selection in the PICOS criteria, and the database searches did not restrict to clinical efficacy outcomes.

A 4. The EAG noticed a disparity in the segments of MEDLINE being searched across the clinical effectiveness searches. The SLRs for Endometrial, Gastric and Biliary cancer appeared to omit searching MEDLINE Epub Ahead of Print. Please confirm if this is the case.

MEDLINE Segments searched	**SLRs**
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily	D.1.2 Small intestine cancer (table 11) D.1.5 Colorectal cancer (table 40)
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)	D.1.1 Endometrial cancer (table 2) D.1.3 Gastric cancer (table 19) D.1.4 Biliary cancer (table 31)

All MEDLINE searches were run via the Ovid platform using search code *ppez* to cover *Ovid MEDLINE(R)* and *Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily*. MSD apologise for the reporting error.

Small Intestine Cancer SLR

A 5. Please explain the rationale for not including terms for pembrolizumab in the searches for the small intestine cancer SLR.

The small intestine cancer SLR was originally conducted (search date: June 2021) to respond to a request for supplementary information (RSI) by the European Medicines Agency as part of the evaluation of the regulatory application that later resulted in the approval of pembrolizumab in previously treated MSI-H tumours. To address the limitation of lack of comparator arm in the registration studies (KEYNOTE-158 and KEYNOTE-164), a comprehensive SLR was conducted on the efficacy of historical standard therapies not limited to any country-specific clinical practice. As such, the search strategy included search terms specific for interventions that were deemed representative of the standard therapies at the time

of the regulatory evaluation and therefore search terms for pembrolizumab were not included.

The search strategy has been revised to include pembrolizumab as search term (please see also response to A6). The new search identified an additional single-arm trial on pembrolizumab in patients with previously treated advanced small bowel adenocarcinoma (2). Of the 40 patients treated with pembrolizumab in the trial, only four had MSI-H tumour.

Patients in this study (regardless of MSI-H status) were older than in KEYNOTE-158 (median age 63 years [29–85] vs 58 [21 to 77]), and a greater number of patients had two prior lines of therapy (67.5% vs 22.2%), but they were similar for proportion of males and race. The study shows better PFS results for MSI-H patients compared to KEYNOTE-158 for the same tumour site whereas median OS was not reached in neither study. However, the results are likely be impacted by the small sample size, (only two PFS and OS events occurred), and should be interpreted with caution.

Table 1 PFS and OS results for KEYNOTE-158 and Pedersen et al. 2021

	KEYNOTE-158 (small intestine cancer), n=27	**Pedersen 2021, n=4**
Median PFS (95% CI), months	23.4 (4.3, NR)	NE (2.5, NE)
Median OS (95% CI), months	NR (16.2, NR)	NE (2.5, NE)

Abbreviations: NE, Not Estimated; NR, Not Reached

A 6. The Evidence Assessment Group (EAG) noted a number of issues with the strategies reported for this SLR. As well as missing synonyms for combined chemotherapy regimen (see Capeox, missing terms include XELOX, CAPOX, CAPE-OX or OxCap) and redundant lines (Line #30 is redundant in the Embase strategy as it is a subset of #35, however this would not impact on recall) the strategies for Embase, MEDLINE and CENTRAL also contained errors regarding line combinations in the interventions facet (see line #34 in the Embase strategy).

Given that a search combining a facet for small intestinal cancer and study design, similar to the searches for the other tumour sites, would have resulted in the smallest overall results set (n=902 without the interventions facet in the Embase search), please rerun these searches in line with the approach taken by

the other SLRs: i.e., small intestine cancer + adapted Scottish Intercollegiate Guidelines Network (SIGN) randomised controlled trial (RCT) filter (Limits: 2000-date/English only) and screen the results to ensure that no relevant papers were missed by the original search.

Due to the limited time available, it was not feasible to remove intervention terms entirely for this search. To capture all potentially relevant studies based on the comparators of interest, we have revised the search strategies with the following changes:

- Added pembrolizumab
- Updated CAPOX (added all synonyms)
- Removed redundant oxaliplatin lines
- Added nab-paclitaxel
- Updated leucovorin synonyms (added folinic acid)

The searches provided below were run on 17 February 2023.

Table 2 Embase Search strategy - Embase 1974 to 2023 February 16 (Ovid); Search executed: 17 February 2023

No.	Terms	Hits
1	exp small intestine tumor/	24847
2	((duoden$ or jejun$ or ile$ or small intestin$ or small bowel$) adj3 (neoplas$ or cancer$ or carcinoma$ or tumo$ or malignan$ or adenocarcinoma$)).ti,ab.	18229
3	(advance$ or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or spread$ or migration$ or progress$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or secondary or incurable or "not curable").mp.	7118050
4	(or/1-2) and 3	16887
5	exp pembrolizumab/	31987
6	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18 or SCH-900475).ti,ab.	17177
7	5 or 6 [pembrolizumab]	33323
8	folfox.mp.	6182
9	exp leucovorin/	41375
10	(leucovorin or calcium folinate or sodium folinate or leucovorin calcium or leucovorin sodium or folinic acid or calcium leucovorin).mp.	43502

11	9 or 10 [leucovorin]	43502
12	exp fluorouracil/	153769
13	(5-fluorouracil or "5 fluorouracil" or adrucil or "5-fu" or "5 fu" or fluoroblastin or fluorolex or "fluorouracil 5" or "nsc 18913" or "nsc18913" or "nsc 19893" or "nsc19893").mp.	58126
14	12 or 13 [5-FU]	159891
15	exp oxaliplatin/	49429
16	(oxaliplatin or eloxatin or aiheng or ai heng or l-ohp or jm-83 or jm83 or jm 83 or rp-54780 or rp54780 or rp 54780 or sr-96669 or sr96669 or sr 96669).mp.	52610
17	15 or 16 [oxaliplatin]	52610
18	11 and 14 and 17	19397
19	8 or 18 [folfox ± bevacizumab]	23034
20	(XELOX or CAPOX or Eloxatin or xeloda or CapeOx or Cape-Ox or OxCap).mp.	6191
21	exp capecitabine/	35481
22	(capecitabine or xeloda or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or r340).mp.	38146
23	21 or 22 [capecitabine]	38146
24	23 and 17 [capecitabine + oxaliplatin]	16274
25	20 or 24 [capeox ± bevacizumab]	19081
26	folfoxiri.mp.	695
27	exp irinotecan/	44115
28	(irinotecan or camptosar or camptothecin-11 or "camptothecin 11" or CPT-11 or "CPT 11").mp.	46361
29	27 or 28 [irinotecan]	46361
30	11 and 14 and 17 and 29	11423
31	26 or 30 [folfoxiri ± bevacizumab]	11856
32	11 and 14 [5-FU + leucovorin ± bevacizumab]	32215
33	exp capecitabine/	35481
34	(capecitabine or xeloda or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or r340).mp.	38146
35	33 or 34 [capecitabine ± bevacizumab]	38146
36	exp paclitaxel/	128482
37	(paclitaxel or anzatax or NSC-125973 or NSC 125973 or NSC125973 or taxol or taxol A or bris taxol or taxol, bris or paxene or praxel or 7-epi-taxol or 7 epi taxol or onxol or nab-paclitaxel or nab paclitaxel or Abraxane or ABI 007 or albumin-bound paclitaxel or nanoparticle paclitaxel or paclitaxel albumin or protein-bound paclitaxel).mp.	135024
38	36 or 37 [paclitaxel]	135024
39	docetaxel/	69844
40	(docetaxel or docetaxel hydrate or docetaxel trihydrate or docetaxol or docetaxel anhydrous or N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol or taxoltere metro or taxotere or NSC 628503 or RP 56976 or RP-56976).mp.	72272
41	39 or 40 [docetaxel]	72272

42	folfiri.mp.	4262
43	11 and 14 and 29	14556
44	42 or 43 [folfiri ± bevacizumab]	17119
45	7 or 19 or 25 or 31 or 32 or 35 or 38 or 41 or 44	256536
46	Clinical Trial/	1065813
47	Randomized Controlled Trial/	762148
48	controlled clinical trial/	467943
49	multicenter study/	361917
50	Phase 3 clinical trial/	67150
51	Phase 4 clinical trial/	5242
52	exp RANDOMIZATION/	98163
53	Single Blind Procedure/	50015
54	Double Blind Procedure/	205336
55	Crossover Procedure/	73401
56	PLACEBO/	396456
57	randomi?ed controlled trial$.tw.	312108
58	rct.tw.	51441
59	(random$ adj2 allocat$).tw.	53100
60	single blind$.tw.	30784
61	double blind$.tw.	240472
62	((treble or triple) adj blind$).tw.	1762
63	placebo$.tw.	360100
64	Prospective Study/	838870
65	single arm.tw.	26375
66	(Phase II or Phase 2).tw.	158886
67	Phase 2 clinical trial/	104111
68	or/46-67	2950859
69	Case Study/	95450
70	case report.tw.	517180
71	abstract report/ or letter/	1293998
72	Conference proceeding.pt.	0
73	Conference abstract.pt.	4677443
74	Editorial.pt.	755586
75	Letter.pt.	1279355
76	Note.pt.	917489
77	or/69-76	8166361
78	68 not 77	2123506
79	4 and 45 and 78	168
80	limit 79 to yr=2000 - current	167
81	limit 80 to english	**16**2

Table 3 MEDLINE Search Strategy - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 16, 2023>; Search executed: 17 February 2023

No.	Terms	Hits

1	exp intestine, small/	167321
2	exp intestinal neoplasms/	260930
3	1 and 2	10436
4	exp duodenal neoplasms/	7380
5	exp ileal neoplasms/	3103
6	exp jejunal neoplasms/	2303
7	((duoden$ or jejun$ or ile$ or small intestin$ or small bowel$) adj3 (neoplas$ or cancer$ or carcinoma$ or tumo$ or malignan$ or adenocarcinoma$)).mp.	21337
8	or/3-7	26062
9	(advance$ or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or spread$ or migration$ or progress$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or secondary or incurable or "not curable").mp.	5144106
10	8 and 9	9855
11	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18 or SCH-900475).ti,ab.	6998
12	folfox.mp.	3514
13	exp leucovorin/	11050
14	(leucovorin or calcium folinate or sodium folinate or leucovorin calcium or leucovorin sodium or folinic acid or calcium leucovorin).mp.	14818
15	13 or 14 [leucovorin]	14827
16	exp fluorouracil/	50519
17	(5-fluorouracil or "5 fluorouracil" or adrucil or "5-fu" or "5 fu" or fluoroblastin or fluorolex or "fluorouracil 5" or "nsc 18913" or "nsc18913" or "nsc 19893" or "nsc19893").mp.	42097
18	16 or 17 [5-FU]	65005
19	exp oxaliplatin/	8054
20	(oxaliplatin or eloxatin or aiheng or ai heng or l-ohp or jm-83 or jm83 or jm 83 or rp-54780 or rp54780 or rp 54780 or sr-96669 or sr96669 or sr 96669).mp.	14958
21	19 or 20 [oxaliplatin]	14958
22	15 and 18 and 21	3775
23	12 or 22 [folfox ± bevacizumab]	5753
24	(XELOX or CAPOX or Eloxatin or xeloda or CapeOx or Cape-Ox or OxCap).mp.	1807
25	exp capecitabine/	5327
26	(capecitabine or xeloda or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or r340).mp.	8648
27	25 or 26 [capecitabine]	8648
28	27 and 21	2536
29	24 or 28 [capeox ± bevacizumab]	3370
30	folfoxiri.mp.	336
31	exp irinotecan/	7952
32	(irinotecan or camptosar or camptothecin-11 or "camptothecin 11" or CPT-11 or "CPT 11").mp.	13105

33	31 or 32 [irinotecan]	13105
34	15 and 18 and 21 and 33	1719
35	30 or 34 [folfoxiri ± bevacizumab]	1926
36	15 and 18 [5-FU + leucovorin ± bevacizumab]	10065
37	exp capecitabine/	5327
38	(capecitabine or xeloda or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or r340).mp.	8648
39	37 or 38 [capecitabine ± bevacizumab]	8648
40	exp paclitaxel/	30373
41	(paclitaxel or anzatax or NSC-125973 or NSC 125973 or NSC125973 or taxol or taxol A or bris taxol or taxol, bris or paxene or praxel or 7-epi-taxol or 7 epi taxol or onxol or nab-paclitaxel or nab paclitaxel or Abraxane or ABI 007 or albumin-bound paclitaxel or nanoparticle paclitaxel or paclitaxel albumin or protein-bound paclitaxel).mp.	46141
42	40 or 41 [paclitaxel]	46141
43	docetaxel/	12080
44	(docetaxel or docetaxel hydrate or docetaxel trihydrate or docetaxol or docetaxel anhydrous or N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol or taxoltere metro or taxotere or NSC 628503 or RP 56976 or RP-56976).mp.	19620
45	43 or 44 [docetaxel]	19620
46	folfiri.mp.	1737
47	15 and 18 and 33	2742
48	46 or 47 [folfiri ± bevacizumab]	3729
49	11 or 23 or 29 or 35 or 36 or 39 or 42 or 45 or 48	84873
50	Randomized Controlled Trials as Topic/	160443
51	randomized controlled trial/	586786
52	Random Allocation/	106906
53	Double Blind Method/	174327
54	Single Blind Method/	32500
55	clinical trial/	537114
56	clinical trial, phase i.pt.	24603
57	clinical trial, phase ii.pt.	39272
58	clinical trial, phase iii.pt.	21391
59	clinical trial, phase iv.pt.	2383
60	controlled clinical trial.pt.	95190
61	randomized controlled trial.pt.	586786
62	multicenter study.pt.	330656
63	clinical trial.pt.	537114
64	exp Clinical Trials as topic/	380441
65	or/50-64	1550598
66	(clinical adj trial$).tw.	463960
67	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	194684
68	PLACEBOS/	35925
69	placebo$.tw.	243325
70	randomly allocated.tw.	35458
71	(allocated adj2 random$).tw.	39163
72	single arm.tw.	12188

73	or/66-72	773133
74	65 or 73	1889124
75	case report.tw.	385137
76	letter/	1207595
77	historical article/	369065
78	or/75-77	1943197
79	74 not 78	1846954
80	10 and 49 and 79	37
81	limit 80 to yr=2000 - current	36
82	limit 81 to english	**34**

Table 4 CENTRAL search strategy - EBM Reviews - Cochrane Central Register of Controlled Trials - January 2023 (Ovid); Search executed: 17 February 2023

No.	Terms	Hits
1	intestine, small/	635
2	intestinal neoplasms/	133
3	1 and 2	8
4	duodenal neoplasms/	66
5	ileal neoplasms/	2
6	jejunal neoplasms/	2
7	((duoden$ or jejun$ or ile$ or small intestin$ or small bowel$) adj3 (neoplas$ or cancer$ or carcinoma$ or tumo$ or malignan$ or adenocarcinoma$)).mp.	581
8	or/3-7	584
9	(advance$ or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or spread$ or migration$ or progress$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or secondary or incurable or "not curable").mp.	566120
10	8 and 9	345
11	(Pembrolizumab or Lambrolizumab or Keytruda or MK-3475 or MK3475 or MK 3475 or L01XC18 or SCH-900475).ti,ab.	2620
12	folfox.mp.	1416
13	leucovorin/	1967
14	(leucovorin or calcium folinate or sodium folinate or leucovorin calcium or leucovorin sodium or folinic acid or calcium leucovorin).mp.	4501
15	13 or 14 [leucovorin]	4501
16	fluorouracil/	5847
17	(5-fluorouracil or "5 fluorouracil" or adrucil or "5-fu" or "5 fu" or fluoroblastin or fluorolex or "fluorouracil 5" or "nsc 18913" or "nsc18913" or "nsc 19893" or "nsc19893").mp.	8017
18	16 or 17 [5-FU]	10890
19	oxaliplatin/	1574

20	(oxaliplatin or eloxatin or aiheng or ai heng or l-ohp or jm-83 or jm83 or jm 83 or rp-54780 or rp54780 or rp 54780 or sr-96669 or sr96669 or sr 96669).mp.	5339
21	19 or 20 [oxaliplatin]	5339
22	15 and 18 and 21	1478
23	12 or 22 [folfox ± bevacizumab]	2468
24	(XELOX or CAPOX or Eloxatin or xeloda or CapeOx or Cape-Ox or OxCap).mp.	1401
25	capecitabine/	1561
26	(capecitabine or xeloda or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or r340).mp.	4547
27	25 or 26 [capecitabine]	4547
28	27 and 21	1519
29	24 or 28 [capeox ± bevacizumab]	2217
30	folfoxiri.mp.	294
31	irinotecan/	1150
32	(irinotecan or camptosar or camptothecin-11 or "camptothecin 11" or CPT-11 or "CPT 11").mp.	3816
33	31 or 32 [irinotecan]	3816
34	15 and 18 and 21 and 33	597
35	30 or 34 [folfoxiri ± bevacizumab]	826
36	15 and 18 [5-FU + leucovorin ± bevacizumab]	3178
37	capecitabine/	1561
38	(capecitabine or xeloda or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or r340).mp.	4547
39	37 or 38 [capecitabine ± bevacizumab]	4547
40	paclitaxel/	4412
41	(paclitaxel or anzatax or NSC-125973 or NSC 125973 or NSC125973 or taxol or taxol A or bris taxol or taxol, bris or paxene or praxel or 7-epi-taxol or 7 epi taxol or onxol or nab-paclitaxel or nab paclitaxel or Abraxane or ABI 007 or albumin-bound paclitaxel or nanoparticle paclitaxel or paclitaxel albumin or protein-bound paclitaxel).mp.	12066
42	40 or 41 [paclitaxel]	12066
43	docetaxel/	2602
44	(docetaxel or docetaxel hydrate or docetaxel trihydrate or docetaxol or docetaxel anhydrous or N-debenzoyl-N-tert-butoxycarbonyl-10-deacetyltaxol or taxoltere metro or taxotere or NSC 628503 or RP 56976 or RP-56976).mp.	8155
45	43 or 44 [docetaxel]	8155
46	folfiri.mp.	1238
47	15 and 18 and 33	1016
48	46 or 47 [folfiri ± bevacizumab]	1875
49	11 or 23 or 29 or 35 or 36 or 39 or 42 or 45 or 48	28586
50	10 and 49	27
51	limit 50 to yr=2000 - current	27
52	limit 51 to english	**27**

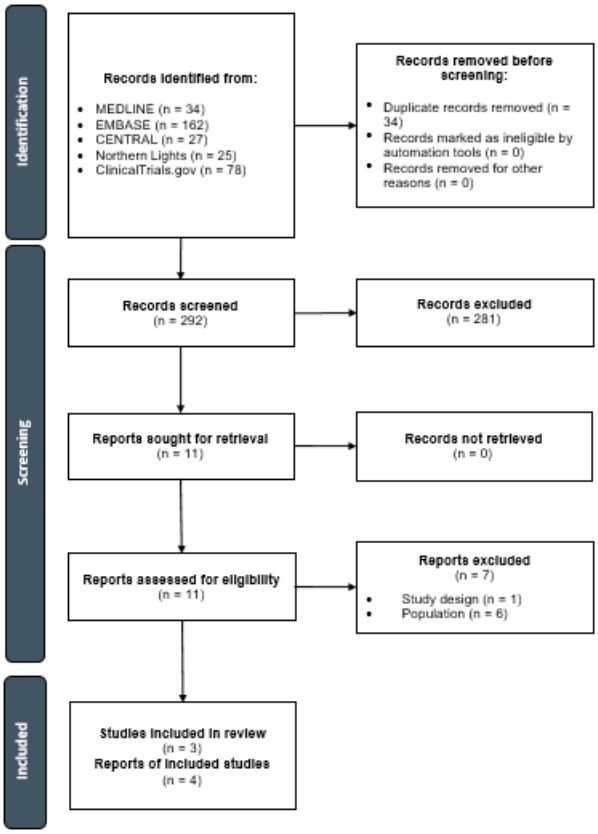
As shown in the table below, after title and abstract screening and full-text selection three additional citations were identified, of which two reported the results of the KEYNOTE-158 study. Pedersen et al. 2021 is discussed in the response to A5.

Author	Year	Journal	Title
Pedersen et al. (2)	2021	Clinical Cancer Research	Zebra: A multicenter phase ii study of pembrolizumab in patients with advanced small-bowel adenocarcinoma
Maio et al. (3)	2022	Annals of Oncology	Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: Updated analysis from the phase ii keynote-158 study
Marabelle et al. (4)	2020	Journal of Clinical Oncology	Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/ mismatch repair-deficient cancer: Results from the phase ii keynote-158 study

A 7. There appeared to be a disparity in the numbers of hits reported for the conference searches between the PRISMA flowchart (n=0) and the strategies listed in Section D1.2.2. (ASCO =19, ESMO=6) confirm the correct numbers.

We have updated the PRISMA flow diagram below to reflect the revised search strategy to address question A6 as well as all citations retrieved from the conference searches (i.e., Northern Lights, n=25).

Figure 1 Updated PRISMA flow diagram



Endometrial Cancer SLR

A 8. The EAG noticed a disparity in the date range reported for the Embase and MEDLINE search strategies in the Endometrial cancer SLR, both had date ranges ending in June 2021 despite the searches being carried out in August 2022, please can you clarify if this is a search error or an error in reporting. If this was a search error, please rerun searches and screen the results to ensure that no relevant papers have been missed.

MSD confirm that an error has been made in reporting the date range for search done using Embase and MEDLINE. The database information in the search strategy heading was not updated from an earlier search. The correct search date range is the following:

Embase: Embase 1974 to 26 August 2022

MEDLINE: MEDLINE(R) In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R) 1946 to 26 August 2022

The searches were conducted on 29 August 2022 as correctly reported in the company submission.

Biliary Cancer SLR

A 9. There appears to be a disparity for the number of search results reported for the conference searching between the strategies listed in Section D1.4.1 (n=225) and the number listed in the PRISMA flow chart (n=370). Please confirm which is correct.

The number in the PRISMA flow diagram (Figure 4 of company submission Appendix) is correct as 370 citations were screened in the biliary SLR.

Two searches for the Northern Lights Databases (ASCO and ESMO) conducted in June 2021 as part of the original SLR were erroneously not included in the Appendix of the company submission and are reported below:

Table 5: Search strategy for Northern Lights Databases - American Society of Clinical Oncology (ASCO) - Northern Light Life Sciences Conference Abstracts 2010 to 2021 Week 24; Search executed: 29 June 2021

No.	Terms	Hits
1	exp bile duct cancer/	378
2	exp gallbladder cancer/	1,133
3	((biliary or bile duct or gallbladder or intrahepatic bile duct or extrahepatic bile duct) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	2,009
4	((biliary or bile duct or gallbladder or intrahepatic bile duct or extrahepatic bile duct) adj3 adenocarcinoma*).ti,ab.	99
5	cholangiocarcinoma*.ti,ab.	2,797
6	or/1-5	5,227
7	(advance$ or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or spread$ or migration$ or progress$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or secondary or incurable or "not curable").mp.	470,088
8	6 and 7	2,201
9	American Society of Clinical Oncology.cf.	64,846
10	8 and 9	231
11	limit 10 to yr = 2020	31
12	limit 10 to yr = 2019	30
13	11 or 12	61

Table 6: Search strategy for Northern Lights Databases - European Society for Medical Oncology (ESMO) - Northern Light Life Sciences Conference Abstracts 2010 to 2021 Week 24; Search executed: 29 June 2021

No.	Terms	Hits
1	exp bile duct cancer/	378
2	exp gallbladder cancer/	1,133

3	((biliary or bile duct or gallbladder or intrahepatic bile duct or extrahepatic bile duct) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	2,009
4	((biliary or bile duct or gallbladder or intrahepatic bile duct or extrahepatic bile duct) adj3 adenocarcinoma*).ti,ab.	99
5	cholangiocarcinoma*.ti,ab.	2,797
6	or/1-5	5,227
7	(advance$ or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or spread$ or migration$ or progress$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or secondary or incurable or "not curable").mp.	470,088
8	6 and 7	2,201
9	European Society for Medical Oncology.cf.	17,544
10	8 and 9	119
11	limit 10 to yr = 2020	16
12	limit 10 to yr = 2019	21
13	11 or 12	37

The search strategies for Northern Lights Databases (ASCO and ESMO) used in September 2022 for the SLR update and presented in the company submission are also reported below.

Table 7 Search strategy for Northern Lights Databases - American Society of Clinical Oncology (ASCO) - Northern Light Life Sciences Conference Abstracts 2010 to 2022 Week 36; Search executed: 22 September 2022

No.	Terms	Hits
1	exp bile duct cancer/	411
2	exp gallbladder cancer/	1,264
3	((biliary or bile duct or gallbladder or intrahepatic bile duct or extrahepatic bile duct) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	2,253
4	((biliary or bile duct or gallbladder or intrahepatic bile duct or extrahepatic bile duct) adj3 adenocarcinoma*).ti,ab.	109
5	cholangiocarcinoma*.ti,ab.	3,198
6	or/1-5	5,901
7	American Society of Clinical Oncology.cf.	71,695
8	6 and 7	473
9	limit 8 to yr = "2020-current"	176

Table 8 Search strategy for Northern Lights Databases - European Society for Medical Oncology (ESMO) - Northern Light Life Sciences Conference Abstracts 2010 to 2022 Week 36; Search executed: 22 September 2022

No.	Terms	Hits
1	exp bile duct cancer/	411
2	exp gallbladder cancer/	1,264
3	((biliary or bile duct or gallbladder or intrahepatic bile duct or extrahepatic bile duct) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	2,253
4	((biliary or bile duct or gallbladder or intrahepatic bile duct or extrahepatic bile duct) adj3 adenocarcinoma*).ti,ab.	109
5	cholangiocarcinoma*.ti,ab.	3,198
6	or/1-5	5,901
7	European Society for Medical Oncology.cf.	18,989
8	6 and 7	193
9	limit 18 to yr = "2020-current"	49

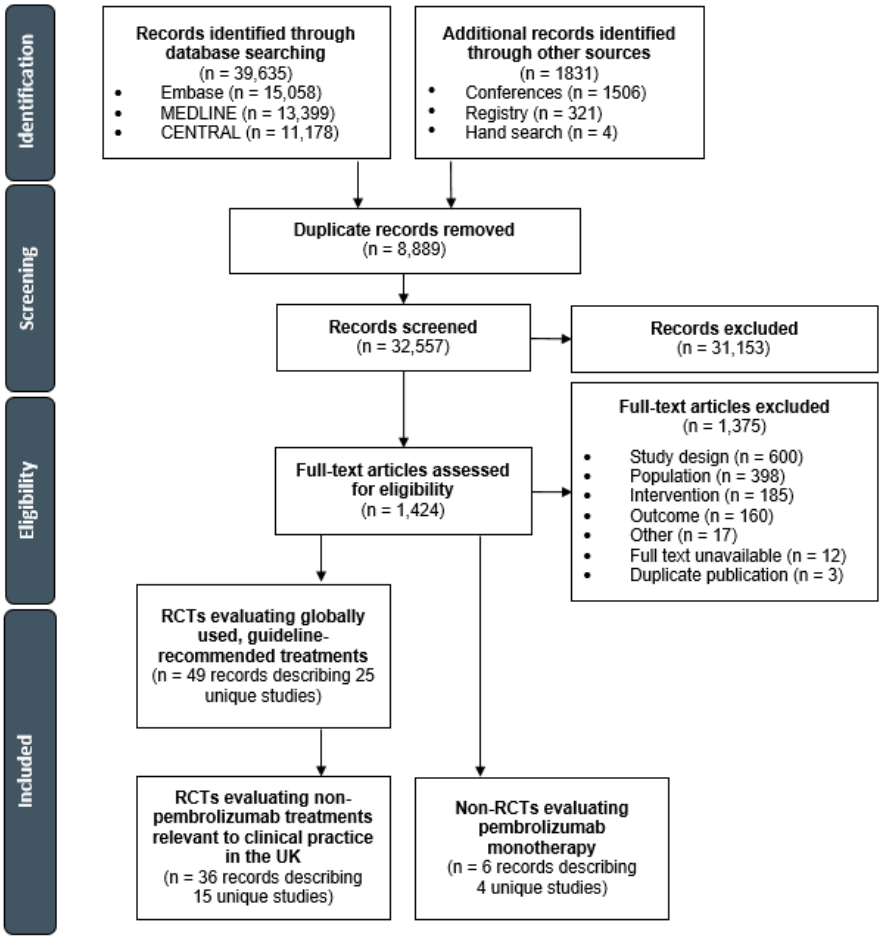
The difference between the number reported on the PRISMA flow diagram and the total number of hits from Tables Table ***5***Table 8 (n=323) can be explained by additional searches that were conducted during both the original and updated SLR. In the original SLR, 29 additional conference abstract citations from ASCO 2021 were added after the original searches were run as they had not yet been indexed in the Northern Lights database.
For the SLR update, 18 additional conference abstract citations from ESMO 2022 were added after the original searches were run as they had not yet been indexed in the Northern Lights database.

Colorectal Cancer SLR

A 10. There appears to be a disparity for the number of search results reported for the conference searching between the strategies listed in Section D1.5.2 (n=1506) and the number listed in the PRISMA flow chart (n=76). Please confirm which is correct.

MSD apologise for the reporting error. The updated PRISMA flow diagram depicting the 1506 conference abstract records retrieved is provided below.

Figure 2 Updated PRISMA flow diagram



For all economics searches (for all conditions)

A 11. The search methods for all economics searches report a search of MEDLINE & Embase via EMBASE.com. Please confirm that this refers to a search of Embase only conducted on the understanding that it contains all records from Medline.

Over 2,800 journals are unique to Embase and 3,000 journal titles are covered by both Embase and MEDLINE. Both sets are indexed by Embase using Emtree. 2,500 journals from MEDLINE are not indexed by Embase using Emtree, but are instead indexed using the MEDLINE thesaurus MeSH. These indexed MEDLINE records are delivered to Elsevier daily. After deduplication, they are incorporated into Embase to produce “MEDLINE-unique records.” These MEDLINE-unique records are not re-indexed by Elsevier. However, their indexing is mapped to Emtree terms. This way, Emtree terms can be used to search all Embase records, including those from MEDLINE, and hence a separate search on MEDLINE is not required.

A 12. Searches reported for all topics had search dates of June 2021. Were any update searches run, and if not what impact might this have had?

Updates to the original economic SLR were not conducted. Given the scale and resources required to complete the original SLR and limited relevant studies identified, a pragmatic targeted literature review was conducted instead which searched for economic evaluations within the target population of interest. This search was conducted on 12 August 2022 with no relevant economic evaluations identified that were consistent with the target population.

Colorectal Cancer economics searches

A 13. In each of the Centre for Reviews and Dissemination (CRD) searches reported for colorectal cancer (Section 2.1.1), there appears to be a reporting error in the final line combination line #15. Should this read "(#14) IN NHSEED, HTA" rather than "(#23) IN NHSEED, HTA"?

There is a typographical error in the search write-ups. The final line combination (#15) should be #14 in NHSEED, HTA.

A 14. The EAG noted an odd use of commas in the reporting of hits per line in the PubMed strategies (Tables 3, 7 & 11), please provide a copy of the original strategies as run in the database.

The use of commas is different in this table due to the difference in styles across geographies. The tables can be updated and presented as per the international system of numeration, with no material difference to results.

Gastric Cancer economics searches

A 15. There appears to be a reporting error in line #7 of each of the Embase strategies (see Table 2 in Section 2.1.1, Table 6 in Section 2.1.2, and Table 10 in Section 2.1.3) The hits reported suggest that this should read "#4 AND #5 AND #6" rather than "#4 OR #5 OR #6", please confirm if this is the case.

This is a typographical error and these lines should read as "#4 AND #5 AND #6".

Small Intestine cancer economics searches

A 16. There appears to be an issue with the reporting of hits per line in the Embase strategy in Table 2 in Section 2.1.1. The error seems to originate in line #14 but the EAG is unclear whether this is just a reporting error. Please provide a copy of the original strategy as run (i.e. as exported from the database rather than copied into a table).

This is a reporting error and should read as follows:

14.	#13 AND [2011-2021]/py	249

Decision Problem

A 17. Priority question: The NICE scope includes 'established management without pembrolizumab' as a valid comparator for all sub-populations (colorectal tumours, endometrial tumours and gastric, biliary, or small intestine tumours). This aspect of the NICE scope implies that any comparator, provided it is currently used in United Kingdom (UK) clinical practice, is a valid comparator. However, 'established management without pembrolizumab' has not been included in the decision problem. If established management options have not been included amongst the specified comparators in the decision problem, this is likely to lead to a biased evaluation of the evidence.

Please list all established clinical management options for each of the tumour sub-populations so the EAG can evaluate if all relevant comparators are included amongst those listed in the decision problem.

Please see responses below including to B4a where deviations from the NICE scope are considered.

A 18. The rationale for not using nivolumab with ipilimumab as a comparator in the decision problem (for the sub-population with colorectal cancer) is not clearly explained, despite this comparator being requested in the National Institute for

Health and Care Excellence (NICE) scope. It does seem that the company accept its use in UK clinical practice even if some patients might not be eligible for it.

a) Please provide a better explanation.

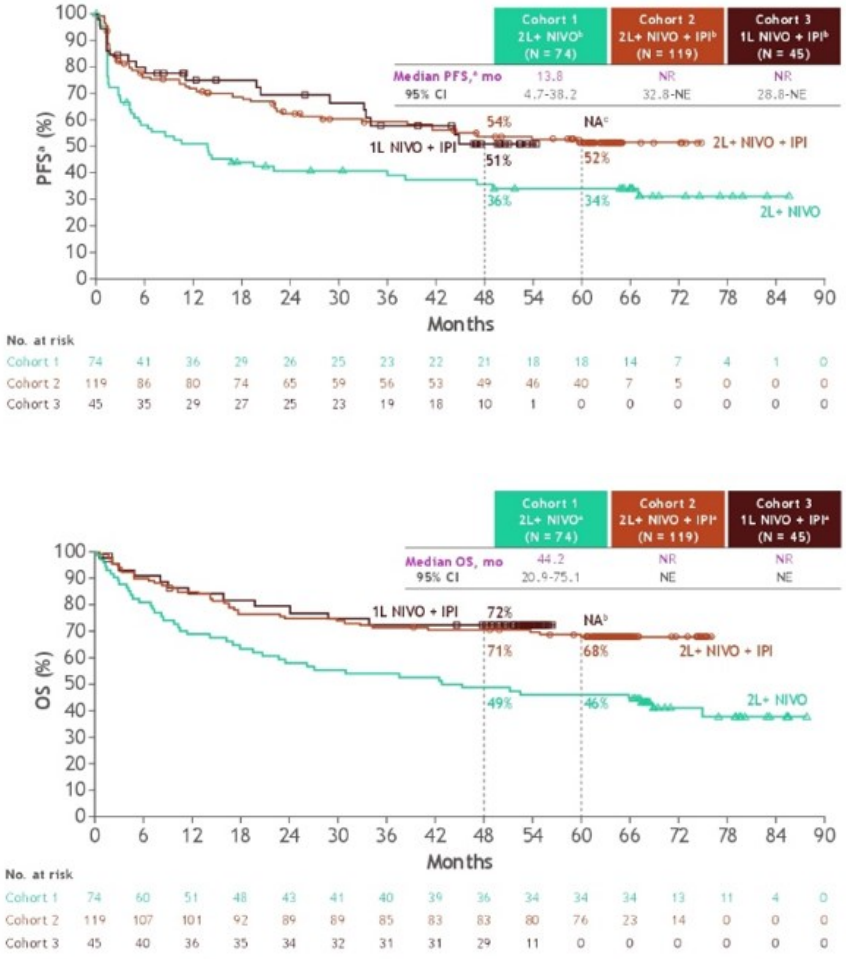
b) Please include nivolumab with ipilimumab as a comparator.

MSD do not believe nivolumab with ipilimumab is a relevant comparator (as described in section B.1.3.4 of document B of company submission). Following the positive recommendation by NICE for nivolumab with ipilimumab in this MSI-H/dMMR CRC population, clinicians have suggested there is very little (if any) unmet need in this very small patient population that would be met by pembrolizumab in MSI-H/dMMR CRC.

Patients are not eligible for nivolumab with ipilimumab if they have previously received an anti-PD-1 antibody therapy such as pembrolizumab (see the Blueteq for this combination (5)). The vast majority of the metastatic MSI-H/dMMR CRC population will receive pembrolizumab in first line ([redacted]). This means only some subset of this [redacted] of patients progress following first line chemotherapy and are eligible for the IO combination here (i.e., those who are fit enough and do not receive BSC).

For this small group clinicians have advised that nivolumab and ipilimumab combination is the choice for clinicians and patients, as opposed to an immunotherapy alone given the better efficacy achieved when adding a CTLA-4 targeting treatment. This is shown by the published efficacy results of the parallel cohorts of nivolumab with ipilimumab and nivolumab alone in the checkmate 142 cohort study (Overman et al. 2018) (6). The ASCO poster showing relatively up to date comparisons between the two arms (and overlayed OS/PFS KM curves, see Figure 3) will be provided with the response.

Figure 3 ASCO poster efficacy results (nivolumab and ipilimumab vs. nivolumab)



It is possible that some of these patients may have a degree of autoimmune related comorbidities which make them unsuitable for a dual immunotherapy and CTLA-4 combination. For these patients, nivolumab with ipilimumab is not the comparator as they are deemed to be unsuitable for the immunotherapy and CTLA-4 combination, meaning the relevant comparator is chemotherapy.

A 19. The rationale for not using single-agent irinotecan and raltitrexed as a comparator in the decision problem (for the sub-population with colorectal cancer), which was requested in the NICE scope, is based on clinical opinion that this agent is rarely prescribed in clinical practice. Please provide more objective evidence to back up the rationale.

Please see response to B4a where these divergences from the scope are discussed in detail – this was based on clinical opinion and previous appraisal consensus.

A 20. Sub-grouping for tumour site and previous treatment were requested by the NICE scope. Sub-grouping for tumour site was carried out where appropriate, but sub-grouping by previous treatment was not attempted, and no reasons were given in the company submission (CS). Please explain the rationale for this and if appropriate provide sub-group analyses for previous treatment.

No subgroup analysis by previous treatment was performed neither in the KEYNOTE-158 nor in the KEYNOTE-164 trials. Considering the small sample size within each tumour type and the inherent exploratory nature of subgroup analyses, no valid and reliable conclusions can be drawn about the effectiveness of the technology in subgroups.

Also, in KEYNOTE-158 the subgroup analysis by previous treatment across the four tumour types would potentially lead to misleading results as it would not take into account the heterogeneity across histologies.

In KEYNOTE-164, two cohorts of patients (Cohort A and B) were enrolled based on previous lines of chemotherapy (at least two lines and one line of fluoropyrimidine-based combination therapies for cohort A and B, respectively). As shown in the response to A34, no substantial differences in prior treatments is seen within and between the two cohorts with 100% of participants being previously treated with fluoropyrimidine-based combination therapies.

Systematic Literature Review

A 21. Priority question: In the SLR for gastric cancer, only RCTs are included. This is at odds with the main clinical evidence submission, where non-randomised and single arm trials are included. Please discuss the limitations of this approach and ensure that all relevant non-randomised and single-arm trials related to gastric cancer are included in the main clinical evidence submission.

While the use and selection of single-arm trials is justified in the context of rare malignancies such as some of the MSI-H cancers, a large amount of evidence was expected to be found in the unselected population with previously treated gastric cancer. Therefore, a pragmatic choice was made to limit the selection to RCTs which would have provided the most robust form of evidence that could be used as the source for comparator efficacy.

Of the 142 studies that were excluded on the basis of the study design (Table 28 of the company submission Appendix), only eight include a comparator of interest (i.e., paclitaxel or FOLFIRI). Of these, four studies evaluated the efficacy of paclitaxel in the unselected population (i.e., regardless of MSI-H status) (7-10). KEYNOTE-061 remained the preferred option as evidence source for paclitaxel, as it includes MSI-H subgroup outcome data that is in line with KEYNOTE-158 for the same tumour site.

Four studies investigated the efficacy of irinotecan, 5-fluorouracil and leucovorin (FOLFIRI). Of these, three studies (11-13) reported time to progression (TTP), instead of PFS, defined as the time calculated from the first day of treatment to the date on which progressive disease was first observed or of the last follow-up. With death not included as an event, equivalence of TTP results to PFS results cannot be assumed and therefore these studies were not considered an appropriate evidence source to use in the ITC.

Roviello et al. 2019 (14) investigated the impact of prior ramucirumab treatment on the efficacy of FOLFIRI as third-line therapy in patients (n=26) with metastatic gastric cancer. As shown in Table 9 below, median PFS and OS are shorter compared to pooled FOLFORI studies used in original ITC and therefore current estimates informing the economic model are likely to be conservative compared to pooled estimates that would include evidence from this study.

Table 9 PFS and OS estimates for FOLFIRI in original ITC and Roviello et al. 2019 (gastric cancer)

	Pooled studies in original ITC	Roviello et al. 2019
Median (95%CI) PFS	3.0 months (2.0, 4.0)	52 days (42, 74)
Median (95% CI) OS	6.7 months (4.1, 8.9)	117 days (94, 154)

In addition, three pembrolizumab studies have been identified, of which one is the pivotal trial for this indication (KEYNOTE-158) (4). Fuchs et al. 2018 evaluated pembrolizumab in patients with previously treated advanced gastric and gastroesophageal junction cancer regardless of MSI-H status (15) whereas Kim et al. 2018 does not provide OS data for the MSI-H subgroup (16). KEYNOTE-158 remain the only study investigating the efficacy of pembrolizumab in the approved gastric indication relevant to this appraisal.

Please see Table 10 below which provides details of the interventions evaluated in each study (studies including an intervention of interest are in bold).

Table 10 Trials included in the global SLR but excluded from the UK SLR

Author	Year	Title	Journal	Intervention
Study designs other than randomized controlled trial (n=142)				
Ajani et al	2002	Irinotecan/cisplatin in advanced, treated gastric or gastroesophageal junction carcinoma	Oncology (Williston Park, N.Y.)	Irinotecan/cisplatin
Ajani et al	2006	A multi-center phase ii study of bms-247550 (ixabepilone) by two schedules in patients with metastatic gastric adenocarcinoma previously treated with a taxane	Investigational New Drugs	Ixabepilone
Al-Batran et al	2007	Mitomycin c, 5-fluorouracil, leucovorin, and oxaliplatin as a salvage therapy for patients with cisplatin-resistant advanced gastric cancer: A phase i dose escalation trial	Onkologie	Mitomycin c, 5-fluorouracil, leucovorin, and oxaliplatin
Baize et al	2009	Phase ii study of paclitaxel combined with capecitabine as second-line treatment for advanced gastric carcinoma after failure of cisplatin-based regimens	Cancer Chemotherapy and Pharmacology	Paclitaxel combined with capecitabine
Bando et al	2016	A multicenter phase ii study of tas-102 monotherapy in patients with pre-treated advanced gastric cancer (epoc1201)	European Journal of Cancer	TAS-102
Bando et al	2018	A phase ii study of nab-paclitaxel in combination with ramucirumab in patients with previously treated advanced gastric cancer	European Journal of Cancer	Nab-paclitaxel+ramucirumab
Bang et al	2011	Phase ii study of sunitinib as second-line treatment for advanced gastric cancer	Investigational New Drugs	Sunitinib
Bang et al	2020	Ramucirumab and durvalumab for previously treated, advanced non-small-cell lung cancer, gastric/gastro-oesophageal junction adenocarcinoma, or hepatocellular carcinoma: An open-label, phase ia/b study (jvdj)	European Journal of Cancer	Ramucirumab + durvalumab
Barone et al	2007	Docetaxel and oxaliplatin combination in second-line treatment of patients with advanced gastric cancer	Gastric Cancer	Docetaxel + oxaliplatin
Berton, et al	2021	Antitumor activity of dostarlimab in patients with mismatch repair-deficient/microsatellite instability-high tumors: A combined analysis of two cohorts in the garnet study	American Society of Clinical Oncology Annual Meeting 2021	Dostarlimab

Author	Year	Title	Journal	Intervention
Catenacci et al	2020	Margetuximab plus pembrolizumab in patients with previously treated, her2-positive gastro-oesophageal adenocarcinoma (cp-mgah22-05): A single-arm, phase 1b-2 trial	Lancet Oncology	Margetuximab + pembrolizumab
Chang et al	2005	Phase ii study of paclitaxel and carboplatin in advanced gastric cancer previously treated with 5-fluorouracil and platinum	Japanese Journal of Clinical Oncology	Paclitaxel + carboplatin
Changsong et al	2022	Safety, tolerability, and preliminary efficacy results in patients with advanced gastric/gastroesophageal junction adenocarcinoma from a phase ib/ii study of cldn18.2 car t-cell therapy (ct041)	American Society of Clinical Oncology Annual Meeting 2022	CT041
Cho et al	2006	Paclitaxel and leucovorin-modulated infusional 5-fluorouracil combination chemotherapy for metastatic gastric cancer	Oncology reports	Paclitaxel + leucovorin-modulated Infusional 5-fluorouracil
Chon et al	2011	Salvage chemotherapy of biweekly irinotecan plus s-1 (biweekly iris) in previously treated patients with advanced gastric cancer	Cancer Chemotherapy and Pharmacology	Irinotecan + S-1
Chun et al	2004	Weekly irinotecan in patients with metastatic gastric cancer failing cisplatin-based chemotherapy	Japanese journal of clinical oncology	Irinotecan
Chung et al	2019	Avelumab (anti-pd-l1) as first-line switch-maintenance or second-line therapy in patients with advanced gastric or gastroesophageal junction cancer: Phase 1b results from the javelin solid tumor trial	Journal for ImmunoTherapy of Cancer	Avelumab
Chung et al	2021	Leap-005: A phase 2 multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors-results from the gastric cancer cohort	American Society of Clinical Oncology Annual Meeting 2021	Lenvatinib + pembrolizumab
Cousin et al	2022	Regomune: A phase ii study of regorafenib plus avelumab in solid tumors-results of the oesophageal or gastric carcinoma (ogc) cohort	American Society of Clinical Oncology Annual Meeting 2022	Regorafenib + avelumab
CT.gov	2005	Study of Irinotecan and Docetaxel in Patients With Metastatic or Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma	Clinicaltrials.gov	Irinotecan + docetaxel

Author	Year	Title	Journal	Intervention
CT.gov	2006	An International Phase 2 Study Of SUS11248 In Patients With Advanced / Metastatic Gastric Cancer Failing Chemotherapy	Clinicaltrials.gov	SUS11248
CT.gov	2008	RAD001 (Everolimus) Salvage Monotherapy in Advanced Gastric Cancer (AGC) Who Failed Standard First-line Treatment	Clinicaltrials.gov	Everolimus
CT.gov	2009	Study of Ixabepilone in Asian Subjects With Unresectable or Metastatic Gastric Cancer	Clinicaltrials.gov	Ixabepilone
CT.gov	2021	Everolimus in Combination With Imatinib in Patients With Glivec Refractory/Resistant Gastrointestinal Stromal Tumors	Clinicaltrials.gov	Everolimus + imatinib
Cutsem et al	2021	Primary analysis of a phase ii single-arm trial of trastuzumab deruxtecan (t-dxd) in western patients (pts) with her2-positive (her2+) unresectable or metastatic gastric or gastroesophageal junction (gej) cancer who progressed on or after a trastuzumab-containing regimen	European Society for Medical Oncology Congress 2021	Trastuzumab deruxtecan
Dai et al	2012	Trastuzumab combined with docetaxel-based regimens in previously treated metastatic gastric cancer patients with her2 over-expression	Hepato-Gastroenterology	Trastuzumab
Dayyani et al	2022	A phase 1b multicenter study of TAS-102 in combination with irinotecan in patients with advanced recurrent or unresectable gastric and gastroesophageal adenocarcinoma after at least one line of treatment with a fluoropyrimidine and platinum-containing regimen	Medical Oncology	TAS-102+ irinotecan
Doi et al	2010	Multicenter phase ii study of everolimus in patients with previously treated metastatic gastric cancer	Journal of Clinical Oncology	Everolimus
Doi et al	2019	A phase i study of the anti-cc chemokine receptor 4 antibody, mogamulizumab, in combination with nivolumab in patients with advanced or metastatic solid tumors	Clinical Cancer Research	Mogamulizumab + nivolumab
Doi et al	2019	Phase 1 trial of avelumab (anti-pd-l1) in japanese patients with advanced solid tumors, including dose expansion in patients with gastric or gastroesophageal junction cancer: The javelin solid tumor jpn trial	Gastric Cancer	Avelumab
Fang et al	2014	Biweekly s-1 plus paclitaxel (spa) as second-line chemotherapy after failure from fluoropyrimidine and platinum in advanced gastric cancer: A phase ii study	Cancer Chemotherapy and Pharmacology	S-1 + paclitaxel

Author	Year	Title	Journal	Intervention
Fuchs et al	**2018**	**Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: Phase 2 clinical keynote-059 trial**	**JAMA Oncology**	**Pembrolizumab**
Fukuoka et al	2020	Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: An open-label, dose-escalation, and dose-expansion phase ib trial (regonivo, epoc1603)	Journal of Clinical Oncology	Regorafenib + S-1
Gao et al	2022	Efficacy of the Low Dose Apatinib plus Chemotherapy on Advanced Gastric Carcinoma	Journal of oncology	Apatinib + chemotherapy
Giuliani et al	2003	Docetaxel as salvage therapy in advanced gastric cancer: A phase ii study of the gruppo oncologico italia meridionale (g.O.I.M.)	Anticancer Research	Docetaxel
Giuliani et al	2005	Irinotecan (cpt-11) and mitomycin-c (mmc) as second-line therapy in advanced gastric cancer: A phase ii study of the gruppo oncologico dell' italia meridionale (prot 2106)	American Journal of Clinical Oncology: Cancer Clinical Trials	Irinotecan + mitomycin-c
Graziano et al	2000	A phase ii study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer	Annals of Oncology	Docetaxel
Hamaguchi et al	2008	A phase ii study of sequential methotrexate and 5-fluorouracil chemotherapy in previously treated gastric cancer: A report from the gastrointestinal oncology group of the japan clinical oncology group, jcog 9207 trial	Japanese Journal of Clinical Oncology	Methotrexate + 5-fluorouracil
Hamaguchi et al	2011	A phase ii study of biweekly mitomycin c and irinotecan combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: A report from the gastrointestinal oncology group of the japan clinical oncology group (jcog0109-di trial)	Gastric Cancer	Mitomycin c + irinotecan
Hartmann et al	2007	Mitomycin c plus infusional 5-fluorouracil in platinum-refractory gastric adenocarcinoma: An extended multicenter phase ii study	Onkologie	Mitomycin c + 5-fluorouracil
He et al	2012	Capecitabine "metronomic" chemotherapy for palliative treatment of elderly patients with advanced gastric cancer after fluoropyrimidine-based chemotherapy	Medical Oncology	Capecitabine
Herbst et al	2019	Ramucirumab plus pembrolizumab in patients with previously treated advanced non-small-cell lung cancer, gastro-oesophageal cancer, or	Lancet Oncology	Ramucirumab + pembrolizumab

Author	Year	Title	Journal	Intervention
		urothelial carcinomas (jvdf): A multicohort, non-randomised, open-label, phase 1a/b trial		
Horita et al	2019	Phase ii clinical trial of second-line weekly paclitaxel plus trastuzumab for patients with her2-positive metastatic gastric cancer	Anti-Cancer Drugs	Paclitaxel + trastuzumab
Imamura et al	2006	Phase ii study of protracted irinotecan infusion and a low-dose cisplatin for metastatic gastric cancer	World Journal of Gastroenterology	Irinotecan + cisplatin
Janjigian et al	2015	Phase ii trial of sorafenib in patients with chemotherapy refractory metastatic esophageal and gastroesophageal (ge) junction cancer	PLoS ONE	Sorafenib
Jeong et al	2008	Phase ii study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (flox regimen) in pretreated advanced gastric cancer	Annals of Oncology	5-fluorouracil, low-dose leucovorin, and oxaliplatin
Jin et al	2005	Biweekly irinotecan and cisplatin as second-line chemotherapy in pretreated patients with advanced gastric cancer: A multicenter phase ii study	Journal of Korean Medical Science	Irinotecan + cisplatin
Jing et al	2021	Apatinib plus S-1 for previously treated, advanced gastric or gastro-oesophageal junction adenocarcinoma: a phase 2, single-arm, prospective study	Journal of Gastrointestinal Oncology	Apatinib + S-1
Jo et al	2012	Phase ii and ugt1a1 genotype study of irinotecan dose escalation as salvage therapy for advanced gastric cancer	British Journal of Cancer	Irinotecan
Jung et al	2020	Safety and efficacy of vactosertib, a tgf-betar1 kinase inhibitor, in combination with paclitaxel in patients with metastatic gastric adenocarcinoma	--	Vactosertib
Jung et al	2022	Multicenter phase ib/ii study of second-line varlitinib and paclitaxel in patients with egfr/her2 co-expressing advanced gastric cancer (k-master-13)	European Society for Medical Oncology Congress 2022	Varlitinib
Kanat et al	2003	Single-agent irinotecan as second-line treatment for advanced gastric cancer	Tumori	Irinotecan
Kang et al	2015	A phase i study of cabazitaxel in patients with advanced gastric cancer who have failed prior chemotherapy (gastana)	Cancer Chemotherapy and Pharmacology	Cabazitaxel
Kang et al	2020	Safety and Tolerability of Bintrafusp Alfa, a Bifunctional Fusion Protein Targeting TGFbeta and PD-L1, in Asian Patients with Pretreated Recurrent or Refractory Gastric Cancer	Clinical Cancer Research	Bintrafusp

Author	Year	Title	Journal	Intervention
Kato et al	2012	Phase ii study of nk105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer	Investigational New Drugs	Nk105
Katsaounis et al	2018	Nab-paclitaxel as second-line treatment in advanced gastric cancer: A multicenter phase ii study of the hellenic oncology research group	Annals of Gastroenterology	Nab-paclitaxel
Katsuya et al	2022	Voyager (kscc1902): A single-arm, multicenter, phase ii study of early induction of nivolumab during second-line treatment with taxane +/- ramucirumab for advanced gastric or gastro-esophageal junction cancer	American Society of Clinical Oncology Annual Meeting 2022	Voyager
Kawamoto et al	2022	Phase II Study of Continued Trastuzumab Plus Irinotecan in Patients with HER2-positive Gastric Cancer Previously Treated with Trastuzumab (HGCSG 1201)	Oncologist	Trastuzumab + irinotecan
Kawamoto et al	2022	Phase II Study of Ramucirumab Plus Irinotecan Combination Therapy as Second-Line Treatment in Patients with Advanced Gastric Cancer: HGCSG1603	Oncologist	Ramucirumab + irinotecan
Kawazoe et al	2021	Safety and activity of trifluridine/tipiracil and ramucirumab in previously treated advanced gastric cancer: An open-label, single-arm, phase 2 trial	The Lancet Gastroenterology and Hepatology	Trifluridine/tipiracil + ramucirumab
Kim et al	2003	Phase ii study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer	Annals of Oncology	Oxaliplatin, 5-fluorouracil and leucovorin
Kim et al	2005	A phase ii study of docetaxel and cisplatin in patients with gastric cancer recurring after or progressing during 5-fu/platinum treatment	Japanese Journal of Clinical Oncology	Docetaxel + cisplatin
Kim et al	**2005**	**Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer**	**British Journal of Cancer**	**Irinotecan, 5-fluorouracil and leucovorin**
Kim et al	**2007**	**A phase ii study of irinotecan with bi-weekly, low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified folfiri) as salvage therapy for patients with advanced or metastatic gastric cancer**	**Japanese Journal of Clinical Oncology**	**Irinotecan + leucovorin + 5-fluorouracil**
Kim et al	**2010**	**A phase ii study of irinotecan, continuous 5-fluorouracil, and leucovorin (folfiri) combination chemotherapy for patients with**	**American Journal of Clinical**	**Irinotecan, + 5-fluorouracil + leucovorin**

Author	Year	Title	Journal	Intervention
		recurrent or metastatic gastric cancer previously treated with a fluoropyrimidine-based regimen	**Oncology : Cancer Clinical Trials**	
Kim et al	2012	A phase ii trial of ixabepilone in asian patients with advanced gastric cancer previously treated with fluoropyrimidine-based chemotherapy	Cancer Chemotherapy and Pharmacology	Ixabepilone
Kim et al	2015	A phase i/ii trial of second-line chemotherapy with paclitaxel and irinotecan in fluoropyrimidine- and platinum-pretreated patients with advanced gastric cancer	Cancer Chemotherapy and Pharmacology	Paclitaxel + irinotecan
Kim et al	**2018**	**Comprehensive molecular characterization of clinical responses to pd-1 inhibition in metastatic gastric cancer**	**Nature Medicine**	**Pembrolizumab**
Kim et al	2019	A phase i/ii study of poziotinib combined with paclitaxel and trastuzumab in patients with her2-positive advanced gastric cancer	Gastric Cancer	Poziotinib + paclitaxel + trastuzumab
Kim et al	2021	Comprehensive molecular characterization of gastric cancer patients from phase ii second-line ramucirumab plus paclitaxel therapy trial	Genome Medicine	Ramucirumab + paclitaxel
Kim et al	2022	Safety and anti-tumor effects of vismodegib in patients with refractory advanced gastric cancer: A single-arm, phase-II trial	Journal of Cancer	Vismodegib
Kimura et al	2011	A phase i study of bi-weekly docetaxel for recurrent or advanced gastric cancer patients whose disease progressed by prior chemotherapy	Japanese Journal of Clinical Oncology	Docetaxel
Kobayashi et al	2006	Phase i study of paclitaxel plus irinotecan combination therapy for patients with refractory and advanced gastric cancer	Alimentary Pharmacology and Therapeutics	Paclitaxel + irinotecan
Kobayashi et al	2020	Phase ii multi-institutional prospective trial of nab-paclitaxel as second-line chemotherapy for advanced gastric cancer refractory to fluoropyrimidine with modified dose reduction criteria (ccog1303)	International Journal of Clinical Oncology	Nab-paclitaxel
Kodera et al	**2007**	**A phase ii study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (ccog0302 study)**	**Anticancer Research**	**Paclitaxel**
Koizumi et al	**2009**	**Second-line chemotherapy with biweekly paclitaxel after failure of fluoropyrimidine-based treatment in patients with advanced or recurrent gastric cancer: A report from the**	**Japanese Journal of Clinical Oncology**	**Paclitaxel**

Author	Year	Title	Journal	Intervention
		gastrointestinal oncology group of the tokyo cooperative oncology group, tcog gc-0501 trial		
Kuboki et al	2021	Phase i study of the irreversible fgfr inhibitor futibatinib in japanese patients with advanced solid tumors: Updated dose expansion results and activity in gastric cancer	European Society for Medical Oncology Congress 2021	Futibatinib
Kunisaki et al	2005	Phase ii study of docetaxel plus cisplatin as a second-line combined therapy in patients with advanced gastric carcinoma	Anticancer Research	Docetaxel + cisplatin
Lee et al	2007	Phase ii study of low-dose paclitaxel and cisplatin as a second-line therapy after 5-fluorouracil/platinum chemotherapy in gastric cancer	Journal of Korean Medical Science	Paclitaxel + cisplatin
Lee et al	2008	A phase ii study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy	Cancer Chemotherapy and Pharmacology	Docetaxel
Lee et al	2009	Phase ii study of s-1 monotherapy in paclitaxel- and cisplatin-refractory gastric cancer	Cancer Chemotherapy and Pharmacology	S-1
Lee et al	2013	Phase ii trial of capecitabine and everolimus (rad001) combination in refractory gastric cancer patients	Investigational New Drugs	Capecitabine + everolimus
Li et al	2021	Subcutaneous envafolimab monotherapy in patients with advanced defective mismatch repair/microsatellite instability high solid tumors	Journal of hematology & oncology	Envafolimab
Li et al	2021	Clinical effectiveness of apatinib at different doses in patients with advanced gastric cancer as the third-line or further treatment: Results from a post-marketing phase iv study	--	Apatinib
Lim et al	2011	Phase i trial of capecitabine plus everolimus (rad001) in patients with previously treated metastatic gastric cancer	Cancer Chemotherapy and Pharmacology	Capecitabine + everolimus
Lin et al	2015	A phase 2 study of fluorouracil/leucovorin in combination with paclitaxel and oxaliplatin as a salvage treatment in patients with refractory or relapsed advanced gastric cancer	Journal of Chemotherapy	Fluorouracil/leucovorin + paclitaxel and oxaliplatin
Liu et al	2017	A multi-center phase ii study and biomarker analysis of combined cetuximab and modified folfiri as second-line treatment in patients with metastatic gastric cancer	BMC Cancer	Cetuximab + FOLFIRI

Author	Year	Title	Journal	Intervention
Lv et al	2014	S-1 monotherapy as second line chemotherapy in advanced gastric cancer patients previously treated with cisplatin/infusional fluorouracil	International journal of clinical and experimental pathology	S-1
Marabelle et al	**2020**	**Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/ mismatch repair-deficient cancer: Results from the phase ii keynote-158 study**	**Journal of Clinical Oncology**	**Pembrolizumab**
Martin-Richard et al	2013	Multicenter phase ii study of oxaliplatin and sorafenib in advanced gastric adenocarcinoma after failure of cisplatin and fluoropyrimidine treatment. A gemcad study	Investigational New Drugs	Oxaliplatin + sorafenib
Mitani et al	2020	A phase ii study of modified folfox6 for advanced gastric cancer refractory to standard therapies	Advances in Therapy	FOLFOX-6
Mochizuki et al	2013	Cpt-11 as a second-line treatment for patients with advanced/metastatic gastric cancer who failed s-1 (ccog0702)	Cancer Chemotherapy and Pharmacology	CPT-11
Moehler et al	2011	An open-label, multicentre biomarker-oriented aio phase ii trial of sunitinib for patients with chemo-refractory advanced gastric cancer	European Journal of Cancer	Sunitinib
Nakajima et al	2021	Multicenter phase i/ii study of nivolumab combined with paclitaxel plus ramucirumab as second-line treatment in patients with advanced gastric cancer	Clinical Cancer Research	Nivolumab + paclitaxel + ramucirumab
Nguyen et al	2006	Epirubicin-docetaxel in advanced gastric cancer: Two phase ii studies as second and first line treatment	Bulletin du cancer	Epirubicin + docetaxel
Nishikawa et al	2017	Phase ii study of the effectiveness and safety of trastuzumab and paclitaxel for taxane- and trastuzumab-naive patients with her2-positive, previously treated, advanced, or recurrent gastric cancer (jfmc45-1102)	International Journal of Cancer	Trastuzumab + paclitaxel
Ocean et al	2014	Phase ii trial of bortezomib alone or in combination with irinotecan in patients with adenocarcinoma of the gastroesophageal junction or stomach	Investigational New Drugs	Bortezomib +/- irinotecan
Oh et al	2016	Phase ii trial of dacomitinib in patients with her2-positive gastric cancer	Gastric Cancer	Dacomitinib
Park et al	2004	Docetaxel plus cisplatin as second-line therapy in metastatic or recurrent advanced gastric cancer progressing on 5-fluorouracil-based regimen	American Journal of Clinical Oncology: Cancer Clinical Trials	Docetaxel + cisplatin

Author	Year	Title	Journal	Intervention
Park et al	2005	Phase i dose-escalating study of docetaxel in combination with 5-day continuous infusion of 5-fluorouracil in patients with advanced gastric cancer	BMC cancer	Docetaxel + 5-fluorouracil
Park et al	2005	Salvage chemotherapy with irinotecan and cisplatin in patients with metastatic gastric cancer failing both 5-fluorouracil and taxanes	Anti-Cancer Drugs	Irinotecan + cisplatin
Park et al	2008	Mitomycin c plus s-1 as second-line therapy in patients with advanced gastric cancer: A noncomparative phase ii study	Anti-Cancer Drugs	Mitomycin c + S-1
Polyzos et al	2006	Subsets of patients with advanced gastric cancer responding to second-line chemotherapy with docetaxel-cisplatin	Anticancer Research	Docetaxel+cisplatin
Ren et al	2021	Efficacy and Safety of Apatinib for Elderly Patients with Advanced or Metastatic Gastric Cancer After Failure of at Least First-Line Chemotherapy: A Multi-Center, Single-Arm, Phase II Study	OncoTargets and therapy	Apatinib
Rino et al	2013	Phase ii study on the combination of irinotecan plus cisplatin as a second-line therapy in patients with advanced or recurrent gastric cancer	Molecular and Clinical Oncology	Irinotecan + cisplatin
Rosati et al	2007	Reduced dose intensity of docetaxel plus capecitabine as second-line palliative chemotherapy in patients with metastatic gastric cancer: A phase ii study	Annals of Oncology	Docetaxel + capecitabine
Roviello et al	**2019**	**The influence of prior ramucirumab treatment on the clinical activity of folfiri as third-line therapy in patients with metastatic gastric cancer**	**Investigational New Drugs**	**FOLFIRI**
Ruan et al	2017	Multicenter phase ii study of apatinib treatment for metastatic gastric cancer after failure of second-line chemotherapy	Oncotarget	Apatinib
Ryu et al	2017	A phase i/iia study of dhp107, a novel oral paclitaxel formulation, in patients with advanced solid tumors or gastric cancer	Oncologist	DHP107
Ryu et al	2022	Phase i study to evaluate the safety, tolerability and preliminary efficacy of rivoceranib plus paclitaxel in advanced gastric or gastroesophageal junction (gej) cancer	European Society for Medical Oncology Congress 2022	Rivoceranib + paclitaxel
Saeed et al	2020	Cabozantinib (cabo) combined with durvalumab (durva) in gastroesophageal (ge) cancer and other gastrointestinal (gi) malignancies: Preliminary phase ib camilla study results	American Society of Clinical Oncology Annual	Cabozantinib + durvalumab

Author	Year	Title	Journal	Intervention
			Meeting 2020	
Sasaki et al	2014	Phase ii trial of nanoparticle albumin-bound paclitaxel as second-line chemotherapy for unresectable or recurrent gastric cancer	Cancer Science	Nab-paclitaxel
Sato et al	2018	A phase ii study of tri-weekly low-dose nab-paclitaxel chemotherapy for patients with advanced gastric cancer	Anticancer Research	Nab-paclitaxel
Schmalenberg et al	2018	Cabagast: Multicentre, phase ii study with cabazitaxel in previously treated patients with advanced or metastatic adenocarcinoma of the esophagogastric junction and stomach	Journal of Cancer Research and Clinical Oncology	Cabazitaxel
Schoennemann et al	2011	Biweekly cetuximab and irinotecan as second-line therapy in patients with gastro-esophageal cancer previously treated with platinum	Gastric Cancer	Cetuximab + irinotecan
Schonnemann et al	2012	Phase ii study of biweekly cetuximab in combination with irinotecan as second-line treatment in patients with platinum-resistant gastro-oesophageal cancer	European Journal of Cancer	Cetuximab + irinotecan
Shin et al	2005	The efficacy of paclitaxel and cisplatin combination chemotherapy for the treatment of metastatic or recurrent gastric cancer: A multicenter phase ii study	The Korean journal of internal medicine	Paclitaxel + cisplatin
Shin et al	2008	Capecitabine and doxorubicin combination chemotherapy as salvage therapy in pretreated advanced gastric cancer	Cancer Chemotherapy & Pharmacology	Capecitabine + doxorubicin
Shitara et al	2019	Trastuzumab deruxtecan (ds-8201a)in patients with advanced her2-positive gastric cancer: A dose-expansion, phase 1 study	The Lancet Oncology	Trastuzumab deruxtecan
Stroes et al	2022	A phase Ib/II study of regorafenib and paclitaxel in patients with beyond first-line advanced esophagogastric carcinoma (REPEAT)	Therapeutic Advances in Medical Oncology	Regorafenib + paclitaxel
Sun et al	2009	Irinotecan plus capecitabine as a second-line treatment after failure of 5-fluorouracil and platinum in patients with advanced gastric cancer	Japanese Journal of Clinical Oncology	Irinotecan + capecitabine
Sun et al	2021	Multicenter phase ib/ii study of second-line trastuzumab, ramucirumab, and paclitaxel in patients with her2-positive advanced gastric or gastroesophageal junction cancer (her-ram study)	American Society of Clinical Oncology Annual Meeting 2021	Trastuzumab + ramucirumab + paclitaxel
Sym et al	2008	A phase ii study of irinotecan and docetaxel combination chemotherapy	Cancer Chemothe	Irinotecan + docetaxel

Author	Year	Title	Journal	Intervention
		for patients with previously treated metastatic or recurrent advanced gastric cancer	rapy and Pharmaco logy	
Takahashi et al	2021	Phase ii study of the reuse of trastuzumab with docetaxel beyond progression after first-line treatment in second-line treatment for unresectable, metastatic gastric cancer (t-core1203)	Tohoku Journal of Experime ntal Medicine	Trastuzumab + docetaxel
Tamura et al	2020	A phase ii trial of dose-reduced nab-paclitaxel for patients with previously treated, advanced or recurrent gastric cancer (ogsg 1302)	Internation al Journal of Clinical Oncology	Nab-paclitaxel
Wang et al	2019	Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a pd-1 antibody in phase ib/ii clinical trial nct02915432	Annals of Oncology	Toripalimab
Werner et al	2013	Phase i study of everolimus and mitomycin c for patients with metastatic esophagogastric adenocarcinoma	Cancer Medicine	Everolimus + mitomycin c
Won et al	2019	Efficacy of combined vegfr1-3, pdgfalpha/beta, and fgfr1-3 blockade using nintedanib for esophagogastric cancer	Clinical Cancer Research	Nintedanib
Yamada et al	**2001**	**Phase ii trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions**	**Annals of Oncology**	**Paclitaxel**
Yamaguchi et al	**2002**	**Phase ii study of paclitaxel with 3-h infusion in patients with advanced gastric cancer**	**Gastric Cancer**	**Paclitaxel**
Yamaguchi et al	2006	Phase i-ii study of biweekly paclitaxel administration with fixed-dose-rate cisplatin in advanced gastric cancer	Gastric Cancer	Paclitaxel + cisplatin
Yamaguchi et al	2018	Ramucirumab for the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy in japanese patients: A phase 2, open-label study	Gastric Cancer	Ramucirumab
Yamaguchi et al	2021	Phase 1 study of the liposomal formulation of eribulin (e7389-lf): Results from the advanced gastric cancer expansion cohort	--	Eribulin
Yang et al	2020	Apatinib combined with docetaxel in second-line treatment of advanced gastric cancer: A prospective clinical study (data updated)	European Society for Medical Oncology Congress 2020	Apatinib

Author	Year	Title	Journal	Intervention
Yoon et al	2012	Phase ii study of everolimus with biomarker exploration in patients with advanced gastric cancer refractory to chemotherapy including fluoropyrimidine and platinum	British Journal of Cancer.	Everolimus
Yoshida et al	2006	Feasibility study of biweekly cpt-11 plus cddp for s-1- and paclitaxel-refractory, metastatic gastric cancer	Anticancer Research	CPT-11 + CDDP
Yoshino et al	2013	Combination phase ii study of weekly paclitaxel and 5'-dfur for unresectable or recurrent gastric cancer	Anticancer Research	Paclitaxel + 5'-dfur
Zhang et al	2012	Combination chemotherapy with paclitaxel, cisplatin and fluorouracil for patients with advanced and metastatic gastric or esophagogastric junction adenocarcinoma: A multicenter prospective study	Chinese Journal of Cancer Research	Paclitaxel + cisplatin + fluorouracil
Zhang et al	2013	A phase ii study of triweekly paclitaxel and capecitabine combination therapy in patients with fluoropyrimidine-platinum-resistant metastatic gastric adenocarcinoma	Journal of Cancer Research and Therapeutics	Paclitaxel + capecitabine
Zhang et al	2015	Pemetrexed for previously treated patients with metastatic gastric cancer: A prospective phase ii study	British Journal of Cancer	Pemetrexed
Zhang et al	2022	Efficacy and safety of second-line therapy with apatinib combined with chemotherapy as second-line therapy in advanced gastric cancer: a single-arm, open-label, prospective, multicenter study	Annals of Translational Medicine	Apatinib + chemotherapy
Zhao et al	2020	Apatinib combined with paclitaxel-based chemotherapy in patients with taxane-resistant advanced gastric cancer: A single-arm exploratory study	Annals of Translational Medicine	Apatinib + chemotherapy
Interventions not relevant for the UK HTA submissions (n=23)				
Bang et al	2017	Efficacy of sequential ipilimumab monotherapy versus best supportive care for unresectable locally advanced/metastatic gastric or gastroesophageal junction cancer	Clinical Cancer Research	Ipilimumab
Bang et al	2018	Phase iii, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: Primary analysis of javelin gastric 300	Annals of Oncology	Avelumab
CT.gov	2015	A Phase 2 Study of Ramucirumab (LY3009806) in Participants With Gastric or Gastroesophageal Junction (GEJ) Cancer	Clinicaltrials.gov	Ramucirumab

Author	Year	Title	Journal	Intervention
CT.gov	2015	A Study of Ramucirumab (LY3009806) in Combination With Paclitaxel in Participants With Gastric Cancer	Clinicaltrials.gov	Ramucirumab
Cui et al	2019	Efficacy and safety of apatinib combined with s-1 in treatment of advanced gastric cancer and its effect on inflammatory response and immune function	Latin american journal of pharmacy	Apatinib + S-1
Fuchs et al	2014	Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (regard): An international, randomised, multicentre, placebo-controlled, phase 3 trial	The Lancet	Ramucirumab
Janjigian et al	2018	Checkmate-032 study: Efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer	Journal of Clinical Oncology	Nivolumab +/- ipilimumab
Kang et al	2017	Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ono-4538-12, attraction-2): A randomised, double-blind, placebo-controlled, phase 3 trial	The Lancet	Nivolumab
Kang et al	2019	Randomized phase iii angel study of rivoceranib (apatinib) + best supportive care (bsc) vs placebo + bsc in patients with advanced/metastatic gastric cancer who failed >=2 prior chemotherapy regimens	European Society for Medical Oncology Congress 2019	Apatinib
Kelly et al	2020	Safety and efficacy of durvalumab and tremelimumab alone or in combination in patients with advanced gastric and gastroesophageal junction adenocarcinoma	Clinical Cancer Research	Durvalumab + tremelimumab
Lee et al	2021	Phase ib/ii open-label, randomised evaluation of second-line atezolizumab (atezo) + linagliptin (lina) vs ramucirumab (ram) + paclitaxel (pac) in morpheus-gastric cancer	European Society for Medical Oncology Congress 2021	Atezolizumab + linagliptin
Li et al	2013	Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: Results from a randomized, placebo-controlled, parallel-arm, phase ii trial	Journal of Clinical Oncology	Apatinib
Li et al	2016	Randomized, double-blind, placebo-controlled phase iii trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction	Journal of Clinical Oncology	Apatinib
Lorenzen et al	2022	FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced	European Journal of Cancer	FOLFIRI + ramucirumab

Author	Year	Title	Journal	Intervention
		or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel - results from the phase II RAMIRIS Study of the German Gastric Cancer Study Group at AIO		
Ohtsu et al	2013	Everolimus for previously treated advanced gastric cancer: Results of the randomized, double-blind, phase iii granite-1 study	Journal of Clinical Oncology	Everolimus
Pavlakis et al	2016	Regorafenib for the treatment of advanced gastric cancer (integrate): A multinational placebo-controlled phase ii trial	Journal of Clinical Oncology	Regorafenib
Rha et al	2022	The first report of k-umbrella gastric cancer study: An open label, multi-center, randomized, biomarker-integrated trial for second-line treatment of advanced gastric cancer (agc)	American Society of Clinical Oncology Annual Meeting 2022	afatinib, GSK263677, Nivolumab, Ramucirumab
Shah et al	2021	Randomized, open-label, phase 2 study of andecaliximab plus nivolumab versus nivolumab alone in advanced gastric cancer identifies biomarkers associated with survival	Journal for Immunotherapy of Cancer	Andecaliximab + nivolumab
Shitara et al	2018	Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (tags): A randomised, double-blind, placebo-controlled, phase 3 trial	The Lancet Oncology	Trifluridine/tipiracil
Shitara et al	2020	Trastuzumab deruxtecan in previously treated her2-positive gastric cancer	New England Journal of Medicine	Trastuzumab deruxtecan
Su et al	2020	Clinical efficacy and safety of apatinib for treating stomach cancer and its effect on serum ca72-4, cea and ca19-9	Acta medica mediterranea	Apatinib
Tougeron et al	2022	The prodige 59-durigast trial: A randomized phase ii study evaluating folfiri plus durvalumab and folfiri plus durvalumab plus tremelimumab in second-line treatment of patients with advanced gastric or gastro-esophageal junction adenocarcinoma	American Society of Clinical Oncology Annual Meeting 2022	FOLFIRI + durvalumab + tremelimumab
Yan et al	2022	Efficacy and safety of intermittent versus continuous dose apatinib plus docetaxel as second-line therapy in patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma: a randomized controlled study	Annals of Translational Medicine	Apatinib + docetaxel

A 22. Priority question: The CS claims that "…except for paclitaxel in gastric cancer and paclitaxel/doxorubicin in endometrial, there were no published data available specifically in MSI-H/dMMR-specific populations." However, the EAG were able to find a trial of nivolumab with ipilimumab in this population.(6)

a) Please comment on the appropriateness of this trial to the decision problem.

b) Please clarify if all studies were examined for subgroup data in the decision problem population.

c) If some relevant clinical effectiveness had been omitted from the CS then please include and perform appropriate indirect comparisons with pembrolizumab.

The study identified by the EAG was not used to perform an indirect treatment comparison as it evaluated an intervention MSD does not consider a relevant comparator in this appraisal for the reasons provided in the response to A18.

The response to A44 provide details on the studies identified in the SLR that include outcome data for the MSI-H/dMMR subgroup. Depending on data availability, MSI-H/dMMR selected sources were prioritised given the licence population.

A 23. In the SLR for endometrial cancer, the specific reasons for the exclusion of 45 trials from the UK-specific SLR are not provided in Table 8 of the appendices. A general reason ("interventions not of interest") is given in the text on page 14 of the appendices, but more detailed reasons for the exclusion of each study would be helpful to allow assessing the validity of the exclusions. Similarly, in the SLR for gastric cancer, 23 trials were omitted from the UK-specific SLR because they were "not of interest".

Please provide specific reasons why each of the 45 trials in the endometrial cancer SLR and the 23 trials in the gastric cancer SLR are 'not of interest'.

The 45 citations excluded from the endometrial cancer UK-specific SLR and 23 citations excluded from the gastric cancer UK-specific SLR were excluded because the interventions evaluated were not relevant to the UK clinical practice. As explained in the Appendix of the company submission, these 'global SLRs' had a

broader scope and interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage ('UK-specific SLR'). This resulted in a number of studies being considered relevant to the 'global SLR' but excluded from the UK-specific SLR as eligibility criteria for the interventions were not met. Tables Table ***11***Table ***12*** below provide details of the interventions evaluated in the excluded studies which were considered not relevant to current clinical practice in the UK.

Table 11 Trials included in the global SLR but excluded from the UK-specific SLR (endometrial cancer SLR)

Trial ID	Registry number	Principal publication	Principal publication title	Intervention
Acevedo-Gade 2014	--	Acevedo-Gadea et al. 2014	Phase I Clinical Trial of the Mammalian Target of Rapamycin Inhibitor Everolimus in Combination With Oral Topotecan for Recurrent and Advanced Endometrial Cancer	Everolimus + topotecan
Aghajanian 2011	--	Aghajanian et al. 2011	Phase II Trial of Bevacizumab in Recurrent or Persistent Endmetrial Cancer: A Gynecologic Oncology Group Study	Bevacizumab
Alvarez 2013	--	Alvarez et al. 2013	Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: A Gynecologic Oncology Group study	Bevacizumab + temsirolimus
BAY 90-6946	--	Patnaik et al. 2016	First-in-human phase i study of copanlisib (bay 80-6946), an intravenous pan-class i phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-hodgkin's lymphomas	Copanlisib
Boers-Sonderen 2014	NCT0098263	Boers-Sonderen et al. 2014	Temsirolimus and pegylated liposomal doxorubicin (PLD) combination therapy in breast, endometrial, and ovarian cancer: phase Ib results and prediction of clinical outcome with FDG-PET/CT	Temsirolimus + doxorubicin
Brown 2010	--	Brown et al. 2010	Combination of Gemcitabine and Cisplatin Is Highly Active in Women With Endometrial Carcinoma	Gemcitabine + cisplatin
Castonguay 2014	--	Castonguay et al. 2014	A phase II trial of sunitinib in women with metastatic or recurrent endometrial carcinoma: A study of the Princess Margaret, Chicago and California Consortia	Sunitinib
Coleman 2012	--	Coleman et al. 2012	A Phase II Evaluation of Aflibercept in the Treatment of Recurrent or Persistent Endometrial Cancer: a Gynecologic Oncology Group study	Aflibercept

Trial ID	Registry number	Principal publication	Principal publication title	Intervention
Coleman 2015	--	Coleman et al., 2015	A phase II evaluation of selumetinib (AZD6244, ARRY-142886), a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group study	Selumetinib
Dhani 2022	--	Dhani et al. 2022	Phase II Trial of Cabozantinib in Recurrent/Metastatic Endometrial Cancer: A Study of the Princess Margaret, Chicago and California Consortia (NCI9322/PHL86)	Cabozantinib
Dizon 2014	NCT01225887	Dizon et al. 2014	A Phase II Evaluation of Nintedanib (BIBF-1120) in the Treatment of Recurrent or Persistent Endometrial Cancer: An NRG Oncology/Gynecologic Oncology Group Study	Nintedanib
ENDORAD	NCT00870337	Ray-Coquard et al. 2013	Everolimus as second- or third-line treatment of advanced endometrial cancer: Endorad, a phase ii trial of gineco	Everolimus
Fleming 2014	--	Fleming et al. 2014	Temsirolimus with or without Megestrol Acetate and Tamoxifen for Endometrial Cancer: a Gynecologic Oncology Group Study	Temsirolimus +/- megestrol acetate
Fracasso 2006	NCT00071929	Fracasso et al. 2006	Phase ii study of oxaliplatin as second-line chemotherapy in endometrial carcinoma: A gynecologic oncology group study	oxaliplatin
Garcia 2008	NCT00085332	Garcia et al. 2008	A phase ii evaluation of weekly docetaxel in the treatment of recurrent or persistent endometrial carcinoma: A study by the gynecologic oncology group	Docetaxel
GARNET	NCT02715284	Oaknin et al. 2020	Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: A nonrandomized phase 1 clinical trial	Dostarlimab
GOG 129-P	--	Dizon et al. 2009	Phase ii trial of ixabepilone as second-line treatment in advanced endometrial cancer: Gynecologic oncology group trial 129-p	Ixabepilone
GOG 229C	--	Leslie et al. 2013	A Phase II Evaluation of Gefitinib in the Treatment of Persistent or Recurrent Endometrial Cancer: A Gynecologic Oncology Group Study	Gefitinib
GOGO-EM2	--	Tanaka et al. 2018	A phase i/ii study of glif combination chemotherapy for taxane/platinum-refractory/resistant endometrial cancer (gogo-em2)	GLIF
Gonzalez 2021	NCT02611024	Gonzalez et al. 2021	Lurbinectedin (LUR) in combination with Irinotecan	Lurbinectedin + irinotecan

Trial ID	Registry number	Principal publication	Principal publication title	Intervention
			(IRI) in patients (pts) with advanced endometrial carcinoma	
Grendys-Jr 2005	--	Grendys Jr et al. 2005	A phase II evaluation of flavopiridol as second-line chemotherapy of endometrial carcinoma: A Gynecologic Oncology Group study	Flavopiridol
Hamed-Abdelkhalek 2013	--	Hamed and Abdelkhalek 2013	Clinical outcome of docetaxel in advanced or metastatic endometrial cancer	Docetaxel
IMMU-132-01 basket trial	NCT01631552	Bardia et al. 2021	Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial	Sacituzumab govitecan
Jackson 2022	--	Jackson et al. 2022	A phase II trial of bevacizumab and rucaparib in recurrent carcinoma of the cervix or endometrium	Bevacizumab + rucaparib
Katsumata 2005	--	Katsumata et al. 2005	Phase II trial of docetaxel in advanced or metastatic endometrial cancer: a Japanese Cooperative Study	Docetaxel
Konstantinopoulos 2020	NCT02912572	Konstantinopoulos et al. 2020	Phase II study of PARP inhibitor talazoparib and PD-L1 inhibitor avelumab in patients (pts) with microsatellite stable (MSS) recurrent/persistent endometrial cancer	Talazoparib + avelumab
Leslie 2012	--	Leslie et al. 2012	Lapatinib and Potential Prognostic Value of EGFR Mutations in a Gynecologic Oncology Group Phase II Trial of Persistent or Recurrent Endometrial Cancer	Lapatinib
Lheureux 2020	NCT03367741	Lheureux et al. 2020	A randomized phase II study of cabozantinib and nivolumab versus nivolumab in recurrent endometrial cancer	Cabozantinib + nivolumab
Madariaga 2021	NCT03016338	Madariaga et al. 2021	Phase II trial assessing niraparib with or without dostarlimab (anti-PD-1) in recurrent endometrial carcinoma.	Niraparib
McMeekin 2009	--	McMeekin et al. 2009	Single-agent trabectedin as second-line therapy of persistent or recurrent endometrial cancer: Results of a multicenter phase ii study	Trabectedin
Miller 2009	--	Miller et al. 2009	A phase ii evaluation of pemetrexed (alimta, ly231514, ind #40061) in the treatment of recurrent or persistent endometrial carcinoma: A phase ii study of the gynecologic oncology	Pemetrexed
Miller 2019	NCT02584478	Miller et al. 2019	Phase ib/iia study assessing the safety and efficacy of adding al3818 (anlotinib) to standard platinum-based chemotherapy in subjects with recurrent or metastatic	Anlotinib

Trial ID	Registry number	Principal publication	Principal publication title	Intervention
			endometrial, ovarian or cervical carcinoma	
NCI9322/PHL86	NCT01935934	Dhani et al. 2020	Phase ii trial of cabozantinib in recurrent/metastatic endometrial cancer: A study of the princess margaret, chicago, and california consortia (nci9322/phl86)	Cabozantinib
Nishio 2018	UMIN00017097	Nishio et al. 2018	A phase ii trial of irinotecan in patients with advanced or recurrent endometrial cancer and correlation with biomarker analysis	Irinotecan
NSGO-PALEO/ENGOT-EN3	NCT02730429	Mirza et al. 2020	A randomised double-blind placebo-controlled phase ii trial of palbociclib combined with letrozole (l) in patients (pts) with oestrogen receptor-positive (er+) advanced/recurrent endometrial cancer (ec): Nsgo-paleo / engot-en3 trial	Palbociclib + letrozole
Oza 2011	--	Oza et al. 2011	Phase II Study of Temsirolimus in women with recurrent or Metastatic Endometrial Cancer: A Trial of the NCIC Clinical Trials Group	Temsirolimus
PHAEDRA (ANZGOG1601)	NCT03015129, ACTRN1261700016336	Antill et al. 2021	Clinical activity of durvalumab for patients with advanced mismatch repair--deficient and repair--proficient endometrial cancer. A nonrandomized phase 2 clinical trial	Durvalumab
Pineda 2020	NCT02549209	Pineda et al. 2020	A big ten cancer research consortium phase ii trial of pembrolizumab with carboplatin and paclitaxel for advanced or recurrent endometrial cancer	Pembrolizumab + carboplatin + paclitaxel
PRIMMO	NCT03192059	De Jaeghere et al. 2022	Pembrolizumab, radiotherapy, and an immunomodulatory five-drug cocktail in pretreated patients with persistent, recurrent, or metastatic cervical or endometrial carcinoma: Results of the phase II PRIMMO study	Pembrolizumab + radiotherapy + Vitamin D + aspirin + lansoprazole + cyclophosphamide + curcumin
Rimel 2021	NCT03660826	Rimel et al. 2021	A Randomized, Phase II Study Comparing Single-Agent Olaparib, Single Agent Cediranib, and the Combination of Cediranib/Olaparib in Women with Recurrent, Persistent or Metastatic Endometrial Cancer	Olaparib + cediranib
Slomovitz 2022	--	Slomovitz et al 2022	A randomized phase II trial of everolimus and letrozole or hormonal therapy in women with advanced, persistent or recurrent endometrial carcinoma: A GOG Foundation study	Everolimus + letrozole
Tait 2011	NCT00820898	Tait et al. 2011	A phase ii study of gemcitabine (gemzar, ly188011) in the treatment of recurrent or persistent endometrial carcinoma: A	Gemcitabine

Trial ID	Registry number	Principal publication	Principal publication title	Intervention
			gynecologic oncology group study	
Vergote 2020a	NCT02025985	Vergote et al. 2020	Phase 2 study of the exportin 1 inhibitor selinexor in patients with recurrent gynecological malignancies	Selinexor
Vergote 2020b	NCT01111461	Vergote et al. 2020	Second-line lenvatinib in patients with recurrent endometrial cancer	Lenvatinib
Wei 2021	NCT04157491	Wei et al. 2021	Anlotinib plus sintilimab in patients with recurrent advanced endometrial cancer: A prospective open-label, single-arm, phase II clinical trial	Anlotinib + sintilimab

Table 12 Trials included in the global SLR but excluded from the UK-specific SLR (gastric cancer SLR)

Author	Year	Title	Journal	Intervention
Interventions not relevant for the UK HTA submissions (n=23)				
Bang et al	2017	Efficacy of sequential ipilimumab monotherapy versus best supportive care for unresectable locally advanced/metastatic gastric or gastroesophageal junction cancer	Clinical Cancer Research	Ipilimumab
Bang et al	2018	Phase iii, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: Primary analysis of javelin gastric 300	Annals of Oncology	Avelumab
CT.gov	2015	A Phase 2 Study of Ramucirumab (LY3009806) in Participants With Gastric or Gastroesophageal Junction (GEJ) Cancer	Clinicaltrials.gov	Ramucirumab
CT.gov	2015	A Study of Ramucirumab (LY3009806) in Combination With Paclitaxel in Participants With Gastric Cancer	Clinicaltrials.gov	Ramucirumab
Cui et al	2019	Efficacy and safety of apatinib combined with s-1 in treatment of advanced gastric cancer and its effect on inflammatory response and immune function	Latin american journal of pharmacy	Apatinib + S-1
Fuchs et al	2014	Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (regard): An international, randomised, multicentre, placebo-controlled, phase 3 trial	The Lancet	Ramucirumab
Janjigian et al	2018	Checkmate-032 study: Efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer	Journal of Clinical Oncology	Nivolumab +/- ipilimumab
Kang et al	2017	Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ono-4538-12, attraction-2): A randomised, double-blind, placebo-controlled, phase 3 trial	The Lancet	Nivolumab

Kang et al	2019	Randomized phase iii angel study of rivoceranib (apatinib) + best supportive care (bsc) vs placebo + bsc in patients with advanced/metastatic gastric cancer who failed >=2 prior chemotherapy regimens	European Society for Medical Oncology Congress 2019	Apatinib
Kelly et al	2020	Safety and efficacy of durvalumab and tremelimumab alone or in combination in patients with advanced gastric and gastroesophageal junction adenocarcinoma	Clinical Cancer Research	Durvalumab + tremelimumab
Lee et al	2021	Phase ib/ii open-label, randomised evaluation of second-line atezolizumab (atezo) + linagliptin (lina) vs ramucirumab (ram) + paclitaxel (pac) in morpheus-gastric cancer	European Society for Medical Oncology Congress 2021	Atezolizumab + linagliptin
Li et al	2013	Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: Results from a randomized, placebo-controlled, parallel-arm, phase ii trial	Journal of Clinical Oncology	Apatinib
Li et al	2016	Randomized, double-blind, placebo-controlled phase iii trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction	Journal of Clinical Oncology	Apatinib
Lorenzen et al	2022	FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel - results from the phase II RAMIRIS Study of the German Gastric Cancer Study Group at AIO	European Journal of Cancer	FOLFIRI + ramucirumab
Ohtsu et al	2013	Everolimus for previously treated advanced gastric cancer: Results of the randomized, double-blind, phase iii granite-1 study	Journal of Clinical Oncology	Everolimus
Pavlakis et al	2016	Regorafenib for the treatment of advanced gastric cancer (integrate): A multinational placebo-controlled phase ii trial	Journal of Clinical Oncology	Regorafenib
Rha et al	2022	The first report of k-umbrella gastric cancer study: An open label, multi-center, randomized, biomarker-integrated trial for second-line treatment of advanced gastric cancer (agc)	American Society of Clinical Oncology Annual Meeting 2022	afatinib, GSK263677, Nivolumab, Ramucirumab
Shah et al	2021	Randomized, open-label, phase 2 study of andecaliximab plus nivolumab versus nivolumab alone in advanced gastric cancer identifies biomarkers associated with survival	Journal for Immunotherapy of Cancer	Andecaliximab + nivolumab
Shitara et al	2018	Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (tags): A randomised, double-blind, placebo-controlled, phase 3 trial	The Lancet Oncology	Trifluridine/tipiracil
Shitara et al	2020	Trastuzumab deruxtecan in previously treated her2-positive gastric cancer	New England Journal of Medicine	Trastuzumab deruxtecan
Su et al	2020	Clinical efficacy and safety of apatinib for treating stomach cancer and its effect on serum ca72-4, cea and ca19-9	Acta medica mediterranea	Apatinib

Tougeron et al	2022	The prodige 59-durigast trial: A randomized phase ii study evaluating folfiri plus durvalumab and folfiri plus durvalumab plus tremelimumab in second-line treatment of patients with advanced gastric or gastro-esophageal junction adenocarcinoma	American Society of Clinical Oncology Annual Meeting 2022	FOLFIRI + durvalumab + tremelimumab
Yan et al	2022	Efficacy and safety of intermittent versus continuous dose apatinib plus docetaxel as second-line therapy in patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma: a randomized controlled study	Annals of Translational Medicine	Apatinib + docetaxel

A 24. In the SLR for gastric cancer, the outcomes of quality of life and adverse events are not included, although these outcomes are in the NICE scope and decision problem. The lack of these outcomes in the SLR means that otherwise relevant studies restricted to these outcomes would not be included. Please add these outcomes to the review and include any additional relevant studies, if required.

The incorrect version of the PICOS table was provided in the company submission. MSD apologise for the reporting error. The actual PICOS table used during study selection included HRQoL and adverse event outcomes as shown below:

Table 13 Study eligibility criteria for the systematic literature review

Criteria	Inclusion criteria	Exclusion criteria
Population	• Patients with advanced (unresectable and/or metastatic) gastric cancer by histology • Patients previously treated for advanced disease • Adults (≥18 years) • ECOG performance status of 0-1 (or equivalent) • Recurrent disease when stage not specified	• Performance status of 2 or higher (or equivalent) • Stage I or II disease • Central nervous system metastasis • Previously treated with anti-PD-1/PD-L1 agents
Interventions*	• Pembrolizumab • 5-FU • 5-FU + methotrexate/leucovorin • FOLFIRI / mFOLFIRI • Irinotecan • Irinotecan + cisplatin • Paclitaxel • Docetaxel • Docetaxel + cisplatin • Docetaxel + oxaliplatin	• Other systemic therapies • Radiation without chemotherapy • Surgical intervention without systemic treatment • Non-pharmacologic treatments (e.g., hyperthermia)
Comparators	• Unrestricted	--

Outcomes	At least one of the following outcomes: • Overall survival • Progression-free survival • Time to disease progression • Duration of response • Objective response • Complete response • Partial response • Stable disease • Progressive disease • Any-cause and treatment-related AEs • Any-cause and treatment-related grade 3-5 AEs • Any-cause and treatment-related serious AEs • Discontinuation due to AEs • Patient-reported outcomes (e.g., EQ-5D, EORTC QLQ-C30)	--
Study design	• Randomised controlled trials	• Non-randomised controlled trials • Single-arm trials • Observational studies • Case reports • Case series
Time	• From 2000 onward	
Language	• English language	

* Following clinical expert consultation, the final list of comparators reflecting current clinical practice in the UK has been narrowed down to paclitaxel and FOLFIRI.

A 25. In the SLR for small intestine cancer, pembrolizumab is not included as an intervention or comparator. Please explain how an SLR that does not include pembrolizumab will be of relevance to this submission.

As explained in the response to A5, the search strategy included search terms specific for interventions that were deemed representative of the standard therapies at the time of the regulatory evaluation and therefore search terms for pembrolizumab were not included. The search strategy has been revised to include pembrolizumab as search term and resulted in the identification of three additional studies. Please see response to A5 and A6 for details of the studies identified.

A 26. In the SLR for colorectal cancer, nivolumab with ipilimumab is included as a comparator, whereas it is not included in the main clinical evidence submission. Please discuss why is it appropriate to include it in the SLR but not in the main clinical evidence submission.

The inclusion of nivolumab with ipilimumab in the SLR eligibility criteria for the interventions/comparators was based on MSD original understanding of the

treatments that pembrolizumab would displace if it was recommended. Further insights into the treatment pathway for colorectal cancer in the metastatic setting and patient eligibility to licensed treatments, allowed MSD to revise the list of relevant comparators of pembrolizumab in this appraisal, which is presented in the decision problem (Table 1 of document B of company submission), and excludes nivolumab with ipilimumab for the reasons described in the response to A18.

A 27. Regarding the gastric cancer SLR,

a) none of the 'included' studies are in the clinical evidence section of the CS. Please provide a clear explanation why these studies were not included in the clinical evidence section of the CS.

b) it is assumed that the 'included studies' were those used in the indirect treatment comparison (ITC). However, this is not clearly explained in CS appendix D. Please provide a clear explanation for how these 'included' studies were used in the submission.

As explained in section D.1.3.6.1 of the company submission Appendix, in the gastric cancer SLR, 24 studies corresponding to 45 publications were considered relevant to this appraisal as evaluating interventions of interest in line with the decision problem. Of the 24 studies, three studies namely Chao et al. 2013 (KEYNOTE-061) (17), Sym et al. 2013 (18) and Moehler et al. 2016 (SUNCASE) (19) were selected and used in the ITC for the reasons explained in the response to A44.

KEYNOTE-061 is a study that investigates the efficacy of pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer. Inclusion of these data in the clinical evidence for pembrolizumab in the relevant MSI-H /dMMR population is discussed in the response to A32.

Clinical Effectiveness

A 28. Priority question: Please provide the latest data-cut for KEYNOTE-158 and include this in the economic model.

The latest data-cut (IA14 - database cutoff date: 12-JAN-2022) from KEYNOTE-158 is described in Section B.2.6.3 of the company submission as well as in Appendix N.

Due to the short time between cleaned data availability and the submission deadline, these data were not originally included in the economic model. For KEYNOTE-164 (colorectal cancer), the data-cut provided in the company submission corresponded to final analysis (FA) i.e., there is not an updated data cut available for this trial.

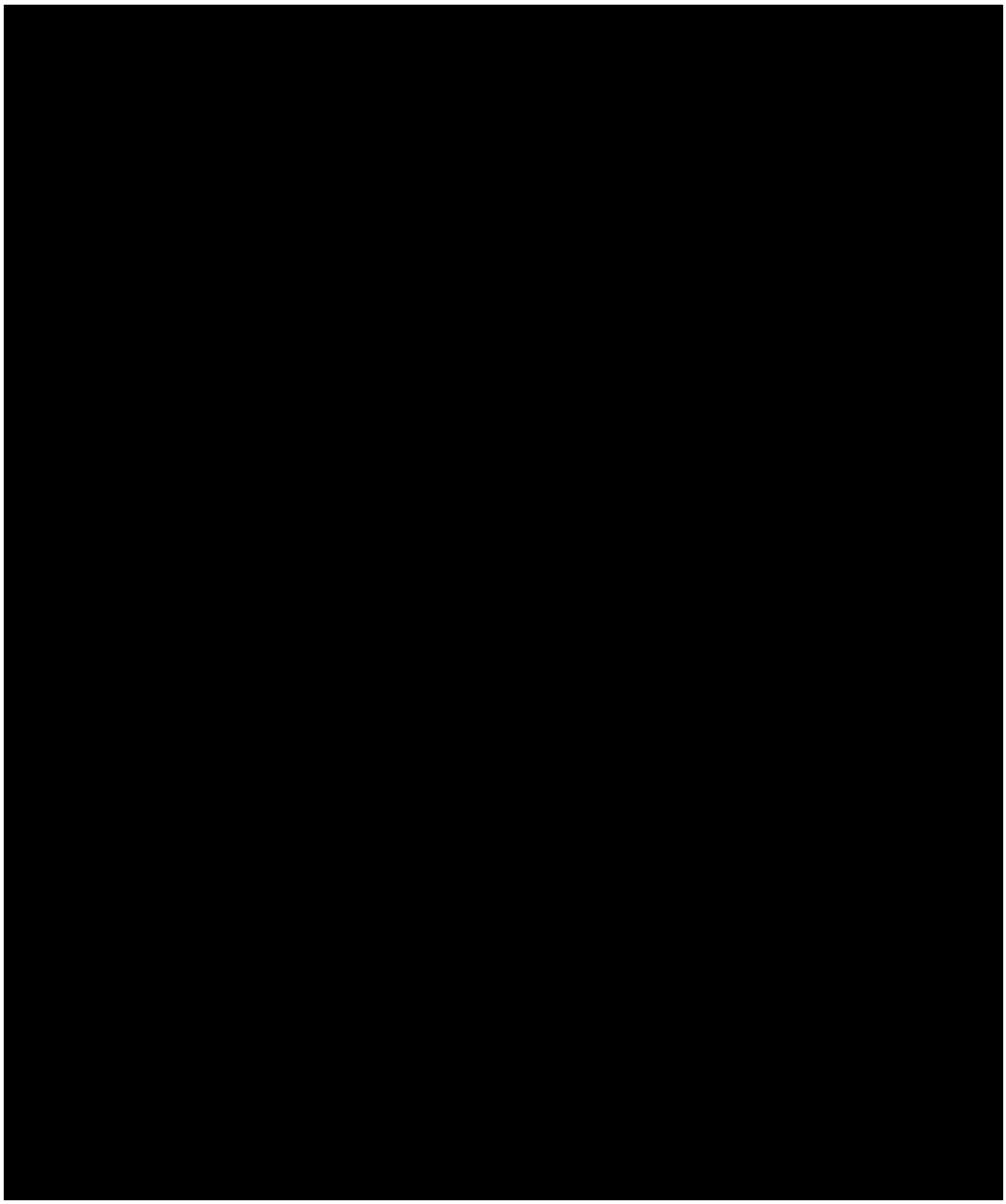
A revised economic model has been provided which includes standard parametric models fitted to IA14 OS, PFS and TTD data (integrated into scenario analysis options). Due to the small number of additional events recorded between IA13 and IA14, the revised analyses have a negligible impact on the ICER – this is because for gastric, biliary, and small intestine the tail is merely extended (there is a small impact on the endometrial site). Due to the time constraints an updated analysis of the BHM using IA14 was not feasible. Given the limited difference shown in the standard parametric models an updated analysis of the BHM is not thought to add value or address existing decision uncertainty. Due to the limitations of unadjusted ITCs and MAIC presented in Section B.2.9 of the CS, these analyses were also not updated using IA14.

In the updated model, at the bottom of the Model Controls sheet (section called “clarification”) the option for using the updated KMs can be selected and when the deterministic results are re-run there is a very minor change in results because of some slight differences in TTD curves. Otherwise, this has no impact on modelled results (i.e. the BHM base-case is still selected) and updated KMs can be viewed in the OS, PFS and TTD sheets when this option is on. When this switch is “yes” the user can also now select PSMs for pembrolizumab in the usual way and these will reflect the PSMs that have been refit to the new data-cut.

To see the impact on efficacy of refitting parametric survival models to this new data cut the user can add the scenario using the button in Model Controls and select “Scenario - KN158 Jan 2022”. This selects the same choice of PSM function by tumour site as the original “Scenario - naïve PSMs” (i.e. the scenario with the originally fitted PSMs). It should be noted that when either PSM scenarios are selected waning is reset to not be included and so this must be re-inputted for each site to match the base-case settings (i.e. waning starting from 84 and ending at 108 months for 100% of patients). The impact is illustrated here:

Tumour site	ICER with original PSMs (with BC waning)	ICER with updated KM and PSMs (with BC waning)
CRC	£8,613	£8,613
Endometrial	£14,670	£15,177
Gastric	£16,929	£17,269
Small Intestine	£17,678	£17,408
Cholangiocarcinoma	£14,706	£15,437
Weighted SoC	£13,283	£13,490

Figure 4 Updated OS, PFS and TTD (IA14 and IA13 KMs overlayed)



A 29. Priority question: Roque et al. 2021 is highlighted as a relevant pembrolizumab trial in the endometrial cancer SLR. Although this was included in the cost effectiveness section of the CS, it was not presented in the clinical effectiveness section.

a) Please explain why this trial was not included as clinical effectiveness evidence in the CS alongside KEYNOTE-158.

b) It appears to the EAG to be in the correct population, so please include it in the clinical effectiveness section and consider pooling with the KEYNOTE-158 endometrial subgroup data.

Roque et al. 2021 refers to a conference abstract for the relevant study of patients with recurrent MSI-H endometrial cancers treated with pembrolizumab. Bellone et al. 2022 provides further data and KM functions for OS and PFS for the same study. This is a small investigator led study of 24 evaluable patients, compared with the 83 endometrial cancer patients observed in KEYNOTE-158.

Patients in Bellone et al. 2022 were older (mean age 69 vs. 64.3) and the majority (50%) were FIGO stage 1 compared to KEYNOTE-158 where endometrial patients were disease stage IV or IVB (97.6%). Also, in Bellone et al. 2022 six patients (25%) harboured Lynch/Lynch- like tumours and 18 (75%) had sporadic endometrial cancer whereas details on the molecular pathways originating MSI-H/dMMR tumours are not available for KEYNOTE-158. Data from this study are therefore uncertain given the small patient population and may represent a healthier but older patient population not thought to be consistent with pivotal trials related to the licence.

Comparison of Bellone et al. 2022 OS data with those from KEYNOTE-158 endometrial cancer patients shows outcomes are comparable although Bellone et al. 2022 has a shorter maximum follow up period. PFS data are similar between the two studies (but slightly improved for Bellone study) and any interpretation of tangible differences between the studies should be treated with caution given the small patient numbers. In summary:

- Median PFS (Bellone study vs KEYNOTE-158): 25.8 months vs. 21.9 months

- Median OS (Bellone study vs KEYNOTE-158): 40 months vs. Not reached
- ORR (Bellone vs KN-158): 58% vs. 50.6%

A 30. Priority question: KEYNOTE-028 was excluded on the basis of dosage from the biliary cancer and colorectal SLRs, and therefore not included in the clinical evidence of the CS. However, the dosage of pembrolizumab is not specified in either the NICE scope nor the decision problem. Please clarify why this trial was omitted from the clinical evidence.

Whilst neither the NICE scope nor the decision problem specify the dosage of pembrolizumab, the scope of this appraisal is to evaluate the clinical effectiveness and cost-effectiveness of pembrolizumab in the licensed indication. According to the Summary of Product Characteristics (SmPC) (20), the recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks, as opposed to 10 mg/kg every 2 weeks administered in KEYNOTE-028. Therefore, efficacy evidence from this study is not relevant to this appraisal as it is not directly applicable to pembrolizumab at the dosage permitted in clinical practice.

In addition, KEYNOTE-028 was conducted in the unselected population (i.e., regardless of MSI status) and only one patient each in the biliary cancer and colorectal cancer cohorts had MSI-H tumour. In light of this, the population of this study is not considered in line with the population of interest to this appraisal and KEYNOTE-158 and KEYNOTE-164 were the only studies identified in the biliary and colorectal SLR, respectively, investigating the efficacy of pembrolizumab in the approved indication relevant to this appraisal.

The tables below present the baseline characteristics of the two cohorts showing the proportion of participants with MSI-H tumour based on the publications identified in the two SLRs.

Table 14 KEYNOTE-028 - Demographics and baseline clinical characteristics (advanced biliary cancer cohort) (21)

KEYNOTE-028	N= 24
Age, median (range), years	64 (43-70)
≥65, n (%)	11 (45.8)
Sex, n (%)	
Male	14 (58.3)

Female	10 (41.7)
Race, n (%)	
White	8 (33.3)
Asian	12 (50.0)
Black or African	1 (4.2)
American	
Missing	3 (12.5)
ECOG performance status	
n (%)	
0	9 (37.5)
1	15 (62.5)
PD-L1 expression,[a] n (%)	
Positive	24 (100.0)
Negative	0
Not evaluable	**0**
MSI-H, n (%)	**1 (4.2)**
Negative	**14 (58.3)**
Missing[b]	9 (37.5)
Histology, n (%)	
Adenocarcinoma	24 (100.0)
Adenosquamous	0
Number of prior lines of therapy, n (%)	
0[c]	0
1	3 (12.5)
2	9 (37.5)
3	10 (41.7)
4	2 (8.3)
≥5	0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; NA, not assessed; PD-L1, programmed death ligand 1.
a The presence of a PD-L1-positive tumor was an enrollment criterion in the KEYNOTE-028 study.
b Reasons for missing MSI status included insufficient tissue for MSI testing, poor quality DNA, testing failure and lack of appropriate consent for necessary genetic testing.
c Includes one patient who received adjuvant, neoadjuvant or definitive therapy only prior to receiving study treatment with pembrolizumab.

Table 15 KEYNOTE-028 - Demographics and baseline clinical characteristics (advanced colorectal cancer cohort) (22)

KEYNOTE-028	***N* = 23**
Median age, years (range)	57 (40–78)
Sex, *n* (%)	
Male	13 (57)
Female	10 (43)
Race, *n* (%)	
White	11 (48)
Asian	6 (26)
Black or African American	2 (9)
Not specified	4 (17)
ECOG performance status, *n* (%)	
0	6 (26)
1	16 (70)
Unknown	1 (4)

MMR mutational status, *n* (%)	
MSS	**22 (96)**
MSI-H	**1 (4)**
Tumor histology, *n* (%)	
Adenocarcinoma	22 (96)
Lieberkuhn adenocarcinoma	1 (4)
Tumor location, *n* (%)	
Colon	16 (70)
Rectum	5 (22)
Cecum	1 (4)
Colon and rectum	1 (4)
Prior adjuvant or neoadjuvant systemic therapy, *n* (%)	11 (48)
Prior lines of therapy for advanced disease, *n* (%)	
0	1 (4)
2	7 (30)
3	7 (30)
4	5 (22)
≥5	3 (13)
Categories of prior therapy for early or advanced disease,* *n* (%)	
Chemotherapy	23 (100)
Monoclonal antibody	18 (78)
Antibody therapy	5 (22)
Investigational therapy	2 (9)
Hormonal therapy	1 (4)
Immunomodulatory therapy	1 (4)
Unknown	2 (9)

Abbreviations: ECOG, Eastern Cooperative Group Oncology Status; MMR, mismatch repair; MSI-H, microsatellite instability-high; MSS, microsatellite-stable.

*Patients may have received ≥1 category of prior therapy.

A 31. Priority question: Le et al. 2015 was excluded on the basis of dosage from the colorectal SLR, and therefore not included in the clinical evidence of the CS. However, the dosage of pembrolizumab is not specified in either the NICE scope or the decision problem. Please clarify why this trial was omitted from the clinical evidence.

Whilst neither the NICE scope nor the decision problem specify the dosage of pembrolizumab, the scope of this appraisal is to evaluate the clinical effectiveness and cost-effectiveness of pembrolizumab in the licensed indication. According to the SmPC (20), the recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks, as opposed to 10 mg/kg every 2 weeks administered in Le et al 2015. In addition, in this study only 11 patients (corresponding to cohort A) had mismatch repair–deficient (dMMR) colorectal cancer. Therefore, efficacy evidence from this small study is not relevant to this

appraisal as it is directly applicable to pembrolizumab at the dosage that will be administered in clinical practice if it was recommended.

A 32. Priority question: KEYNOTE-061 is an RCT that evaluates pembrolizumab versus paclitaxel in people with gastric solid tumours. A sub-group analysis is included for the relevant MSI-H / dMMR population. Why have these data not been included as a key part of the clinical evidence? Please include the comparative evidence of this trial and also use it to inform the economic model.

KEYNOTE-061 and the associated publication appendices contain a small MSI-H post-hoc subgroup analysis (15 pembrolizumab arm patients vs 51 in KEYNOTE-158). PFS and OS outcomes for this analysis group appear better than the results in KEYNOTE-158, based on comparisons of medians and the KM curves.

The base-case model used standard independently fitted PSMs to model comparator efficacy sources (including the MSI-H subgroup in the base-case comparison with paclitaxel). In the table below, a comparison of the naïve ITC analysis presented in the CS comparing KEYNOTE-158 pembrolizumab gastric cancer patients with KEYNOTE-061 paclitaxel patients (Section B.2.9.1) is made with a within trial comparison of KN-061 and indicates that the current estimates informing the economic model are conservative. These estimates show that the small sample in KEYNOTE-061 performs better than the gastric cohort in KEYNOTE-158. This suggests that ICER estimates would be improved for this population if KEYNOTE-061 were included.

An option has been included within the updated economic model to explore the likely impact on cost-effectiveness results. By setting the gastric paclitaxel option for both OS and PFS to “ITC HR” in the Model Controls sheet and selecting the “KN-061 within” (new option at the end of Model Controls sheet) this scenario can be inputted. Results should be interpreted with caution given that the proportional hazards assumption likely does not hold. Results are complicated given that both QALY weights applied in gastric, treatment waning and the impact of worse paclitaxel outcomes all interact and can have complex effects. However, in general results with this fixed-HR scenario improve cost-effectiveness results for pembrolizumab (i.e. compared with the base-case where PSMs are fit to the paclitaxel data from KEYNOTE-061).

Table 16. Relative effects of pembrolizumab versus paclitaxel in gastric cancer, a comparison of unadjusted ITC estimates using KN-158 versus a within trial analysis of KN-061

Outcome	Pembrolizumab versus. paclitaxel hazard ratio (95% CI)	
	KEYNOTE-158 vs. KN-061	KEYNOTE-061 within trial comparison
OS median (95%CI), months	0.52 (0.25-1.09)	0.42 (0.13-1.31)
PFS median (95%CI), months	0.73 (0.36-1.51)	0.54 (0.19-1.54)

A 33. Priority question: KEYNOTE-164 does not include health-related quality of life (HRQoL) as an outcome, despite this being in the NICE scope and the decision problem.

a) Please provide an explanation for the lack of this key outcome

b) If quality of life data exists for this trial, please provide them, and use them to inform the economic model.

At the time of the study design, the KEYNOTE-164 trial was not a Merck-sponsored study and was funded by John Hopkins Center. As such, the trial was not originally designed as a registration study (i.e., to be used in Marketing Authorisation application) and did not aim to collect additional outcome data, such as health-related quality of life.

Overall, comprehensive evidence demonstrating the efficacy and safety of pembrolizumab in patients with previously treated MSI-H/dMMR CRC was provided to EMA for regulatory evaluation, which resulted in the Marketing Authorisation in this indication.

A 34. Priority question: The population in KEYNOTE-158 appears slightly broader than the NICE scope and decision problem because the exact nature of previous standard treatment is not specified (in contrast to the NICE scope and decision problem, where the previous treatments, specific to each cancer type, are

detailed). Please provide the previous treatments given for each separate cancer type in KEYNOTE-158.

The previous treatments, specific to each cancer type, detailed in the NICE scope are based on the Marketing Authorisation that was granted to pembrolizumab in the relevant indication as follows:

KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer **after previous fluoropyrimidine-based combination therapy**.

KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- advanced or recurrent endometrial carcinoma, who have disease progression on or following **prior treatment with a platinum-containing therapy** in any setting and who are not candidates for curative surgery or radiation;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least **one prior therapy**

Tables Table ***17***-Table ***19*** present the prior systemic treatments of participants in KEYNOTE-158 (Cohort K) and KEYNOTE-164 (Cohorts A and B) trials, respectively, for the tumour sites relevant to this appraisal. These show that prior treatments were in line with the NICE scope and Marketing Authorisation, with the vast majority (92.8%) of patients with endometrial cancer receiving platinum-based chemotherapy and 100% of patients with colorectal cancer in both Cohorts A and B receiving fluoropyrimidine-based combination therapy as prior line of chemotherapy regimen. Patients with biliary (cholangiocarcinoma), gastric and small intestine received chemotherapy regimens that are also considered representative of the standard of care in the UK.

Table 17 Participants with Prior Systemic Treatment – KEYNOTE-158 (Cohort K) (ASaT Population)

Prior Systemic Treatment	Tumor Type n (%)

Gemcitabine and Cisplatin Gemcitabine and Oxaliplatin Gemcitabine and Capecitabine Other chemo Total prior systemic therapy	Cholangiocarcinoma (N=22) 14 (63.6) 5 (22.7) 0 1 (4.5) 20 (91%)
Carboplatin Cisplatin Other chemo Total prior systemic therapy	Endometrial (N=83) 75 (90.4) 2 (2.4) 6 (7.2) 83 (100%)
Fluorouracil-containing Regimen Paclitaxel or Carboplatin Capecitabine and Oxaliplatin Other chemo Total prior systemic therapy	Gastric (N=51) 28 (54.9) 9 (17.6) 9 (17.6) 5 (9.8) 51 (100%)
Oxaliplatin and Fluorouracil and Leucovorin Irinotecan and Fluorouracil and Leucovorin Other chemo Total prior systemic therapy	Small Intestine (N=27) 16 (59.3) 1 (3.7) 8 (29.6) 25 (93%)
(Database Cutoff Date: 15OCT2021).	

Table 18 Participants With Specific Prior Oncologic Therapies - KEYNOTE-164 (Cohort A) (ASaT Population)

KEYNOTE-164	Pembrolizumab 200 mg n (%)
Subjects in population	61
With one or more systemic therapies	61 (100.0)
Chemotherapy	61 (100.0)
Biologics	53 (86.9)
Other	16 (26.2)
Summary of Prior Systemic Oncologic Therapies	
Chemotherapy	**61 (100.0)**
Fluoropyrimidine (S1, 5FU or capecitabine)	61 (100.0)
Prior Oxaliplatin	58 (95.1)
Prior irinotecan	58 (95.1)
detoxifying agent for antineoplastic	47 (77.0)
Biologics	**53 (86.9)**
Anti-EGFR	31 (50.8)
Cetuximab (or Erbitux)	25 (41.0)
Panitumumab (or Vectibix)	10 (16.4)
Anti-angiogenic	45 (73.8)
Bevacizumab (or Avastin)	45 (73.8)
Ziv-Aflibercept (or Zaltrap)	4 (6.6)
Other	**16 (26.2)**
Regorafenib (or Stivaga)	5 (8.2)

Trifluridine/tipirafcil (or Lonsurf)	3	(4.9)
Other including experimental therapies	9	(14.8)
Every subject is counted a single time for each applicable row and column. (Database Cutoff Date: 19FEB2021).		

Table 19 Participants With Specific Prior Oncologic Therapies - KEYNOTE-164 (Cohort B) (ASaT Population)

KEYNOTE-164	Pembrolizumab 200 mg n	 (%)
Subjects in population	63	
With one or more systemic therapies	63	(100.0)
Chemotherapy	63	(100.0)
Biologics	44	(69.8)
Other	11	(17.5)
Summary of Prior Systemic Oncologic Therapies		
Chemotherapy	**63**	**(100.0)**
Fluoropyrimidine (S1, 5FU or capecitabine)	63	(100.0)
Prior Oxaliplatin	61	(96.8)
Prior irinotecan	41	(65.1)
detoxifying agent for antineoplastic	52	(82.5)
Biologics	**44**	**(69.8)**
Anti-EGFR	19	(30.2)
Cetuximab (or Erbitux)	7	(11.1)
Panitumumab (or Vectibix)	13	(20.6)
Anti-angiogenic	34	(54.0)
Bevacizumab (or Avastin)	34	(54.0)
Ziv-Aflibercept (or Zaltrap)	1	(1.6)
Other	**11**	**(17.5)**
Regorafenib (or Stivaga)	5	(7.9)
Trifluridine/tipirafcil (or Lonsurf)	2	(3.2)
Other including experimental therapies	7	(11.1)
Every subject is counted a single time for each applicable row and column. (Database Cutoff Date: 19FEB2021).		

A 35. Priority question: In both trials (KEYNOTE 158 and KEYNOTE-164), people with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 2 or more were excluded, despite this exclusion not being specified by the NICE scope or the proposed decision problem. This effectively narrows the decision problem relative to the NICE scope.

a) Please provide a rationale for this decision

b) Please provide details of the number of patients excluded from analysis for this reason

Clinical trials evaluating pembrolizumab, as well as other immunotherapies, commonly exclude patients with ECOG PS >1 due to poor level of fitness and comorbidities that make these patients less suitable for this type of treatment. Even though the licence does not specifically restrict pembrolizumab to patients with ECOG 0-1, the Blueteq system f includes performance status as an eligibility criterion for patients to access pembrolizumab based on participant eligibility criteria from the supporting clinical trials, in addition to any other limitations imposed as part of the Marketing Authorisation (5). Therefore, even though NICE final scope does not explicitly restrict patient eligibility based on performance status, this eligibility criterion will be included in the Blueteq form if pembrolizumab is recommended for the indication subject to this appraisal. Also, this exclusion criterion in KEYNOTE-158 and KEYNOTE-164 is in line with current clinical practice in the UK in relation to the treatment with pembrolizumab.

A 36. Although the method of follow up for the outcome of overall survival (OS) is outlined in the CS, the timing and method of follow up for progression-free survival (PFS), duration of response (DOR) and HRQoL is unclear for both KEYNOTE-158 and KEYNOTE-164. Please provide information on the timing and method of follow up for all outcomes.

Details on timing and method of follow-up for PFS, DOR and HRQoL ae provided below for the KEYNOTE-158 and KEYNOTE-164 trials.

KEYNOTE-158

In participants who discontinue study therapy without local site confirmed disease progression (PD), a radiologic evaluation is performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. Every effort is made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 ± 7 days) in the first year and every 24 weeks (168 ± 7days) after year 1 until (1) the start of new anticancer treatment, (2) disease progression per local site assessment, (3) death, or (4) the end of the trial, whichever occurs first. All tumour imaging

(scheduled and unscheduled) should be submitted to the central imaging vendor for analysis. In addition, if the investigator obtains additional imaging, including other modalities, that are obtained at an unscheduled time point to determine if the participant has progressed as well as imaging obtained for other reasons but captures radiologic progression, all of these imaging scans should be sent to the central imaging vendor.

Patient-reported outcomes (PROs) are assessed at every cycle for the first 4 cycles, then every 3 cycles until 9 months, then every 4 cycles until PD while the participant is receiving study treatment, at the Treatment Discontinuation Visit, and at the 30-day Safety Follow-up Visit (the visit schedule should be Cycle 1, 2, 3, 4, 7, 10, 14, 18, 22, etc.). If the Treatment Discontinuation Visit occurs 30 days after the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, PROs do need to be repeated.

KEYNOTE-164

In participants who discontinue study therapy without confirmed PD by the site per irRECIST, tumour imaging is performed at the time of treatment discontinuation (± 4 weeks). In participants who discontinue trial treatment due to documented disease progression, this is the final required tumour imaging. If previous tumour imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumour imaging at treatment discontinuation is not required. In participants who discontinue trial treatment without documented disease progression, every effort is made to continue monitoring their disease status by radiologic imaging using the same imaging schedule of every 9 weeks (Q9W) for the first year, every 12 weeks (Q12W) thereafter to monitor disease status until the start of new anti-cancer treatment, disease progression, death, or the end of the study, whichever occurs first.

A 37. Please provide details of the 18 countries in KEYNOTE-158, and the ten countries in KEYNOTE-164, where data were collected. Please also provide the numbers from each country.

The KEYNOTE-158 trial was conducted in the following 18 countries (number of patients is provided in brackets): Australia (n=[redacted]), Brazil (n=[redacted]), Canada (n=[redacted]),

Colombia (n=[redacted]), Denmark (n=[redacted]), France (n=[redacted]), Germany (n=[redacted]), Israel (n=[redacted]), Italy (n=[redacted]), Japan (n=[redacted]), Mexico (n=[redacted]), Netherlands (n=[redacted]), Norway (n=[redacted]), Republic of Korea (n=[redacted]), Russian Federation (n=[redacted]), Spain (n=[redacted]), South Africa (n=[redacted]), and the United States (n=[redacted]).

The KEYNOTE-164 trial was conducted in the following 10 countries: Australia (n=[redacted]), Belgium (n=[redacted]), Canada (n=[redacted]), France (n=[redacted]), Germany (n=[redacted]), Israel (n=[redacted]), Japan (n=[redacted]), Republic of Korea (n=[redacted]), Spain (n=[redacted]) and the United States (n=[redacted])

A 38. An 'all subjects as treated' (ASaT) approach was used in both trials, whereby a participant was only included in the analysis if at least one dose of the drug had been taken. This may limit the representativeness of the trial to the real-world, where some patients may not take a single dose, and may therefore over-estimate efficacy.

a) Please comment on the rationale for this decision.

b) Please provide details of the number of patients excluded from analysis for this reason.

In the KEYNOTE-158 trial, all participants allocated to Cohort K after screening received at least one dose of study intervention and were therefore analysed in the ASaT population for efficacy analysis. No patient was excluded from the analysis.

In the KEYNOTE-164 trial (Cohort A), of 74 participants screened, 61 were enrolled. The 13 participants who were not enrolled were screen failures (i.e., did not meet inclusion/exclusion criteria). All participants enrolled received at least one dose of study treatment and were therefore analysed in the ASaT population. In the KEYNOTE-164 (Cohort B), of 74 participants screened, 63 were enrolled. The 11 participants who were not enrolled were screen failures (i.e., did not meet inclusion/exclusion criteria). All participants enrolled received at least one dose of study treatment and were therefore analysed in the ASaT population. No patient was excluded from the analysis.

As no patient was excluded from the analysis, the ASaT population in both trials includes the same number of participants that were allocated to the trial arm after

screening (“ITT population”) (Table 20). As such, same efficacy results would be expected if the ITT population had been used in the analysis.

Efficacy analysis in the ITT population (i.e. study participants analysed based on initial treatment assignment and not on the treatment actually received) is the preferred method of statistical analysis in the randomised controlled trials (RCTs) as it preserves randomisation and prevents bias that might be introduced if switching to the other study treatment does not occur randomly. This is not applicable to single-arm trials where, by definition, participants will be analysed based on the only study treatment to which they can be allocated. The evaluation of the treatment effect in the ASaT population is therefore considered appropriate as it reduces the risk of underestimating the efficacy that would occur if participants that were not administered a single dose of study treatment were included in the analysis, especially given the small sample size in some tumour sites.

Table 20 KEYNOTE-158 and KEYNOTE-164 Analysis Population

	Participants allocated (ITT population)	Participants analysed (ASaT population)
KEYNOTE-158 Cohort K (Population with 4 tumor types)	183	183
Endometrial	83	83
Gastric	51	51
Small intestine	27	27
Biliary (Cholangiocarcinoma)	22	22
KEYNOTE-164 (Cohort A + Cohort B) – colorectal	124	124

A 39. In order to allow evaluation of the representativeness of the baseline characteristics of the trial participants to the UK target population, please provide, where known, the characteristics of the UK target population (stratified by endometrial, colorectal, gastric, biliary and small intestine) in terms of age, race,

cancer stage, metastasis stage, number of prior lines of therapy, prior radiation therapy, and programmed death ligand 1 (PD-L1) status.

Limited information on MSI-H patients is available. However, clinical experts when consulted at the advisory board raised no concerns in relation to the representativeness of the trial population to the UK target population.

The following information is based on relevant tumour types regardless of MSI status and stage of cancer. Though these cancers can occur in adults of any age, the rates of diagnosis generally increase with age and rise steeply from age 50. In the UK in 2016-2018, on average each year half of new cases (50%) were in people aged ≥75 and ≥70 for gastric and small intestine cancers, respectively, whereas about 60% of new cases were in people aged ≥70 and ≥65 for colorectal and endometrial cancers, respectively (23-26); more than half of new cases (53%) of gallbladder cancer were in people aged 75 and over (27). As presented in the company submission, there is evidence to suggest Lynch syndrome-associated colorectal carcer has an earlier age of onset, with a crude median age at diagnosis of 52 years versus 69 years in sporadic disease. This may also be associated with earlier detection of Lynch syndrome due to cascade genetic testing in families where other members have already been diagnosed with Lynch-syndrome-associated cancers.

With the exception of endometrial cancer, the majority of the population diagnosed are male. Incidence rates are lower in non-white minority ethnic groups compared with the white group in all relevant tumour sites (Table 21 - same information on age, and sex was also presented in Table 4 section B.1.3.1 of company submission).

Table 21 Incidence statistics by age, sex and ethnic group for each tumour site, all MSI status

	Peak rate of diagnosis in the UK	Proportion of females diagnosed in England	Number (%) of cases by broad ethnic group in England, 2013–2017 (annual average)
Colorectal cancer	85–89	44%	White (90%) Asian (2.1%) Black (1.4%) Mixed/multiple (0.3%)
Endometrial cancer	75–79	100%	White (86%) Asian (4.1%) Black (2.2%) Mixed/multiple (0.5%)

Gastric cancer	85–89	35%	White (88%) Asian (3.0%) Black (2.7%) Mixed/multiple (0.5%)
Small intestine cancer	80–84	45%	White (89%) Asian (3.1%) Black (2.1%) Mixed/multiple (<20 cases)
Biliary cancer	(gallbladder cancer) 85–89	(gallbladder cancer) 71%	(gallbladder cancer) White (84%) Asian (6.1%) Black (2.8%) Mixed/multiple (<20 cases)
Source: Cancer Research UK for age and sex (23-27), Delon et al. 2022 (28) for ethnicity			

A structured literature review conducted to estimate the prevalence of MSI-H and dMMR across solid tumours, found that prevalence was consistently lower at stages 3-4 compared to early stages across tumour sites (29). In particular, for colorectal cancer the prevalence in stages 3-4 was 9% (3%–16%) based on four studies whereas it was higher for stages 1-2 (20% [10%–32%] based on four studies), which is consistent with data reported in Table 3 of the company submission.

In absence of targeted therapies recommended for most of the patients with MSI-H/dMMR solid tumours, standard of care for these patients is based on guidelines and treatment recommendations for MSS/pMMR patients with the same tumour type. Therefore, no differences in prior lines of therapy, prior radiation therapy are expected compared to MSS/pMMR patients. As the current standard of care for MSI-H/dMMR patients do not require PD-L1 testing, including immunotherapies such as pembrolizumab in untreated patients and nivolumab with ipilimumab and dostarlimab in previously treated patients that have been recommended in patients regardless of PD-L1 status, data on PD-L1 status are not available.

A 40. The quality assessment of the trials using the Newcastle-Ottawa scale yielded a ‘low risk of bias’ (section B.2.5). Please elaborate how this rating was reached and explain how single arm trials can be at low risk of bias.

The Newcastle-Ottawa scale was used to evaluate the quality of the KEYNOTE-158 and KEYNOTE-164 trials based on study group representativeness and selection as well as ascertainment of outcomes of interest and adequacy of follow-up.

Whilst acknowledging the limitations of single-arm trials, the representativeness of the study population, the independent central radiologic assessment of outcomes and the adequacy of follow-up methods, as described in section B.2.3. and B.2.4 of the company submission, are indicative of a low risk of bias across these domains. Therefore, the KEYNOTE-164 and KEYNOTE-158 trials met the criteria for high ratings (i.e., score 1) on the Newcastle-Ottawa scale domains and the total score is overall indicative of high quality (Table 22).

Table 22 Risk of bias assessment of KEYNOTE-158 and KEYNOTE-164 trials

Trial ID	Selection				Comparability	Outcomes			Final score
	1	2	3	4	1	1	2	3	
KEYNOTE-158	1	NA	1	1	NA	1	1	1	6
KEYNOTE-164	1	NA	1	1	NA	1	1	1	6

Indirect Treatment Comparison

A 41. Priority question: The ITC uses comparator trials that are not in the H-MSI or dMMR population. The company stated that the estimates from such an ITC would produce conservative estimates of relative efficacy because *"…evidence suggests that MSI-H/dMMR apatients may have worse outcomes compared to patients with MSS or pMMR disease"* (p. 70).

a) Please provide the references to back up the statement that "MSI-H/dMMR patients may have worse outcomes compared to patients with MSS or pMMR disease".

b) Please update the ITC with any additional data obtained in response to question A22.

c) To improve comparability, please perform all ITCs where the pembrolizumab trials are more like those of the comparators i.e., not using KEYNOTE-158 or KEYNOTE-164. This might also enable an anchored ITC, which will further reduce the risk of bias.

In the health condition section of document B (B.1.3.1) a number of studies are summarised that suggest MSI-H/dMMR status is associated with a poorer prognosis in advanced cancers. These studies relate to the tumour sites for which there is more published evidence available (CRC, Endometrial, Gastric).

At the ad-board there was a consensus that MSI-H/dMMR status is potentially a negative prognostic factor; however, there was more consensus that MSI-H/dMMR status is a treatment effect modifier for immunotherapies (i.e. they will be more efficacious in MSI-H/dMMR patients other things being equal).

The KEYNOTE-158 and KEYNOTE-164 trials are considered the most relevant sources to inform pembrolizumab efficacy, given that they are the pivotal trials related to the licence.

The only additional relevant pembrolizumab study is KEYNOTE-061 in gastric cancer, which is a double-arm study comparing pembrolizumab with paclitaxel (one

of the relevant comparators in this tumour site) and therefore this is the source of efficacy used to inform the independent parametric curves for this comparator in the base-case model as explained in section B.2.9 and B.3.3.3.2 (the ITC comparison option is also available in the model).

As explained in response to A32 the relevant sample is a small subgroup from a larger trial (15 MSI-H/dMMR patients vs 51 in the relevant KEYNOTE-158 cohort) and this post-hoc analysis of MSI-H/dMMR patients provides pembrolizumab efficacy data (response, PFS and OS) that is significantly better than the relevant group in KEYNOTE-158 and so it can be argued the current modelling analysis for this comparison is conservative. A simple scenario analysis is provided that applies this within-study treatment effect from KEYNOTE-061 in the model.

A 42. Priority question: No description is given in the CS about the specific methodology used to obtain the literature used in the ITC and the matching-adjusted indirect comparison (MAIC). It appears likely, however, that the SLRs described in the CS appendices were the source of the literature. Please confirm that this is the case.

MSD confirm that evidence source for the ITC and MAIC were obtained from the SLRs conducted for each of the tumour site of interest in this appraisal. The response to A44 outlines which studies were selected for the ITC from the studies identified in the SLR along with the rationale.

A 43. Priority question: It is important to be sure that the comparators used in the ITC/MAIC analyses (outlined in Table 29 of the CS) concur with the decision problem. This appears to be the case for colorectal, gastric and biliary cancer, but not for endometrial or small intestine cancer. For endometrial cancer, the decision problem includes carboplatin as a comparator, but this is absent from the ITC/MAIC analyses (Table 29). For small intestine cancer, the decision problem includes FOLFORI/FOLFOX but Nab-paclitaxel is used in the ITC/MAIC analyses instead (Table 29). These two departures from the decision problem mean that the ITC/MAIC analyses for endometrial and small intestine cancer would not be relevant to the decision problem.

a) Please explain these departures from the decision problem.

b) Please ensure that the comparators in the ITC are those in the decision problem.

Please see the response to question B4a and e which discusses these deviations from the NICE scope in detail.

A 44. Priority question: Although all the studies in Table 29 of the CS are derived from the SLRs, it is not clear if there were additional studies yielded by the SLRs that might also have been relevant (in terms of the comparators listed in Table 29) for inclusion in the ITC/MAIC analyses. For example, it is unclear why Hirai 2004 and Homesley 2008 (to list just 2 examples), were not included in the ITC/MAIC for endometrial cancer. Both studies evaluated paclitaxel which was the comparator listed for endometrial cancer in Table 29. Please explain the rationale for selection of studies for the ITC/MAIC.

The rationale for the selection of studies for the ITC/MAIC is provided below for each tumour site relevant to this appraisal. In particular, MSI-H/dMMR selected sources were prioritised given the licence population. The selected source of efficacy was used to inform the independent parametric models (PSMs) used in the base-case and the ITCs/MAICs that were explored.

Endometrial cancer

Table 23 (corresponding to Table 7 in the Appendix of the company submission) presents the studies that meet the SLR eligibility criteria. Of the 16 included studies, four clinical trials (three single-arm trials and one RCT) evaluating pembrolizumab have been identified, of which KEYNOTE-146 and KEYNOTE-775 investigated the efficacy and safety of pembrolizumab in combination with lenvatinib and therefore are not in line with the intervention of interest in this appraisal (pembrolizumab monotherapy). Roque 2021 is discussed in the response to A29.

Of the thirteen comparator studies, only KEYNOTE-775 includes outcome data for participants with dMMR tumours. The remainder of the studies were conducted in the unselected population and therefore were not selected as the efficacy source for the relevant comparator given the lack of outcomes specifically reported for MSI-H/dMMR patients. It should be noted that, with regard to the population, the SLR eligibility criteria were broader, due to the paucity of evidence anticipated for the

MSI-H/dMMR population, to include studies in the unselected population that could be used as a source for comparator efficacy. However, studies in the MSI-H/dMMR population where available would be prioritised for the reasons above. As such, KEYNOTE-775 was the only evidence source for relevant comparator (physician's choice of paclitaxel or doxorubicin) used as the source for comparator efficacy.

Table 23 List of publications included in the UK-specific SLR (endometrial cancer)

Trial ID	Registry number	Principal publication	Principal publication title	Associated publications
Angioli 2007	--	Angioli et al. 2007 (30)	Liposome-encapsulated doxorubicin citrate in previously treated recurrent/metastatic gynecological malignancies	--
Hirai 2004	--	Hirai et al. 2004 (31)	Phase II trial of 3-h infusion of paclitaxel in patients with adenocarcinoma of endometrium: Japanese Multicenter Study Group	--
Homesley 2008	--	Homesley et al. 2008 (32)	A phase ii trial of weekly 1-hour paclitaxel as second-line therapy for endometrial and cervical cancer	--
KEYNOTE-146/Study 111	NCT02501096	Makker et al. 2020 (33)	Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer	Makker et al. 2019a (34); Makker et al. 2019b (35); Makker et al. 2020 (36)
KEYNOTE-158	NCT02628067	O'Malley et al. 2019 (37)	Pembrolizumab in patients with msi-h advanced endometrial cancer from the keynote-158 study	Maio et al. 2022 (3), O'Malley et al. 2022 (37), O'Malley et al. 2022 (38),
KEYNOTE-775	**NCT03517449**	**Lorusso et al. 2021 (39)**	**Health-related quality of life (HRQoL) in advanced endometrial cancer (aEC) patients (pts) treated with lenvatinib plus pembrolizumab or treatment of physician's choice (TPC).**	Colombo et al. 2021 (40), Colombo et al.

Trial ID	Registry number	Principal publication	Principal publication title	Associated publications
				2021 (41), Makker et al. 2022 (42), Makker et al. 2022 (43), Makker et al 2021 (44), Makker et al. 2022 (45), Yonemori et al. 2022 (46)
Lincoln 2003	--	Lincoln et al. 2003 (47)	Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: A gynecologic oncology group study	--
McMeekin 2015	NCT00883116	McMeekin et al. 2015 (48)	Phase iii randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer	CT.gov 2015 (49)
Muggia 2002	--	Muggia et al. 2002 (50)	Phase ii trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: A gynecologic oncology group study	--
Nishio 2003	--	Nishio et al. 2003 (51)	Weekly 1-h paclitaxel infusion in patients with recurrent endometrial cancer: A preliminary study	--
Roque 2021	NCT02899793	Roque et al. 2021 (52)	A phase II evaluation of pembrolizumab in recurrent microsatellite instability-high (MSI-H) endometrial cancer patients with Lynch-like versus MLH-1 methylated characteristics (NCT02899793)	Bellone 2021 (53), Bellone 2022 (54)
Scambia 2020	NCT02725268	Scambia et al. 2020 (55)	Randomized phase ii study of sapanisertib (sap) + paclitaxel (pac) versus pac alone in patients (pts) with advanced, recurrent, or persistent endometrial cancer	CT.gov 2020a (56)
Vandenput 2009	--	Vandenput et al. 2009 (57)	Leuven Dose-Dense Paclitaxel/Carboplatin Regimen in Patients With Primary Advanced or Recurrent Endometrial Carcinoma	--
Vandenput 2012	--	Vandenput et al. 2012 (58)	Weekly paclitaxel-carboplatin regimen in patients with primary advanced or recurrent endometrial carcinoma	--

Trial ID	Registry number	Principal publication	Principal publication title	Associated publications
Van-Wijk 2003	--	Van Wijk et al. 2003 (59)	Phase ii study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the eortc gynaecological cancer group	--
Vergote 2015	--	Vergote et al. 2015 (60)	Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: A study in 108 patients by the Belgian Gynaecological Oncology Group	--

Small intestine cancer

The only included study evaluated nab-paclitaxel that is not considered a relevant comparator. Due to the absence of evidence, outcomes from the only identified study were used in the cost-effectiveness analysis as a 'proxy' for the relevant comparators (see response to B4).

Gastric cancer

Table 27 in the Appendix of the company submission presents the studies that meet the SLR eligibility criteria. As explained in section D.1.3.6.1 of the Appendix, based on current understanding of the clinical practice in the UK following clinical expert consultation, 24 studies (RCTs) corresponding to 45 publications are considered relevant to this appraisal (Table 24).

Two studies (SUNCASE and Sym 2013) evaluated the efficacy of (m)FOLFIRI and were used in the ITC. Of the 22 studies on paclitaxel, only KEYNOTE-061 includes outcome data for participants with MSI-H/dMMR tumours. The remainder of the studies were conducted in the unselected population and therefore were deprioritised as a source of efficacy for paclitaxel comparator. It should be noted that, with regard to the population, the SLR eligibility criteria were broader, due to the paucity of evidence anticipated for the MSI-H/dMMR population, to include studies in the unselected population that could be used in the absence of data in the relevant subgroup. As such, KEYNOTE-061 was the only evidence source for the relevant comparator efficacy (paclitaxel).

Table 24 List of publications included in the UK-specific SLR for relevant comparators (gastric cancer)

Trial	Primary or secondary	Author, year	Title
KEYNOTE-061	Primary	Shitara, 2018 (61)	Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (keynote-061): A randomised, open-label, controlled, phase 3 trial
	Secondary	Shitara, 2021 (62)	Molecular determinants of clinical outcomes with pembrolizumab versus paclitaxel in a randomized, open-label, phase 3 trial in patients with gastroesophageal adenocarcinoma
	Secondary	Fuchs, 2020 (63)	Pembrolizumab versus paclitaxel for previously treated patients with pd-l1-positive advanced gastric or gastroesophageal junction cancer (gc): Update from the phase iii keynote-061 trial
	Secondary	**Chao, 2021 (17)**	**Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the keynote-059, keynote-061, and keynote-062 clinical trials**
	Secondary	Van Cutsem, 2021 (64)	Health-related quality of life in advanced gastric/gastroesophageal junction cancer with second-line pembrolizumab in KEYNOTE-061
	Secondary	Cutsem, 2019 (65)	Impact of pembrolizumab (pembro) versus paclitaxel on health-related quality of life (hrqol) in patients with advanced gastric or gastroesophageal junction (gej) cancer that has progressed after first-line chemotherapy (keynote-061)
	Secondary	Fuchs 2022 (66)	Pembrolizumab versus paclitaxel for previously treated PD-L1-positive advanced gastric or gastroesophageal junction cancer: 2-year update of the randomized phase 3 KEYNOTE-061 trial
RAINBOW	Primary	Wilke, 2014 (67)	Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (rainbow): A double-blind, randomised phase 3 trial
	Secondary	Al-Batran, 2016 (68)	Quality-of-life and performance status results from the phase iii rainbow study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric or gastroesophageal junction adenocarcinoma
	Secondary	Cascinu, 2021 (69)	Tumor response and symptom palliation from rainbow, a phase iii trial of ramucirumab plus paclitaxel in previously treated advanced gastric cancer
	Secondary	De Vita, 2019 (70)	Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: Subgroup analysis from rainbow study
	Secondary	Kim, 2018 (71)	Exposure-response relationship of ramucirumab in east asian patients from rainbow: A randomized clinical trial in second-line treatment of gastric cancer

Trial	Primary or secondary	Author, year	Title
	Secondary	Muro, 2016 (72)	Subgroup analysis of east asians in rainbow: A phase 3 trial of ramucirumab plus paclitaxel for advanced gastric cancer
	Secondary	Shitara, 2016 (73)	Subgroup analyses of the safety and efficacy of ramucirumab in japanese and western patients in rainbow: A randomized clinical trial in second-line treatment of gastric cancer
	Secondary	Van Cutsem, 2020 (74)	Biomarker analyses of second-line ramucirumab in patients with advanced gastric cancer from rainbow, a global, randomized, double-blind, phase 3 study
	Secondary	Yamaguchi, 2021 (75)	Quality of life associated with ramucirumab treatment in patients with advanced gastric cancer in japan: Exploratory analysis from the phase iii rainbow trial
	Secondary	Muro, 2019 (76)	Is ramucirumab and paclitaxel therapy beneficial for second-line treatment of metastatic gastric or junctional adenocarcinoma for patients with ascites? Analysis of rainbow phase 3 trial data
	Secondary	Muro, 2018 (77)	Age does not influence efficacy of ramucirumab in advanced gastric cancer: Subgroup analyses of regard and rainbow
	Secondary	Klempner, 2020 (78)	Impact of frontline doublet versus triplet therapy on clinical outcomes: Exploratory analysis from the rainbow study
SHINE	Primary	Van Cutsem, 2017 (79)	A randomized, open-label study of the efficacy and safety of azd4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with fgfr2 polysomy or gene amplification
Sym 2013	**Primary**	**Sym, 2013 (18)**	**A randomized phase ii study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mfolfiri) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy**
Shitara 2014	Primary	Shitara, 2014 (80)	Randomised phase ii study comparing dose-escalated weekly paclitaxel vs standard-dose weekly paclitaxel for patients with previously treated advanced gastric cancer
TyTAN	Primary	Satoh, 2014 (81)	Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of her2-amplified advanced gastric cancer in asian populations: Tytan - a randomized, phase iii study
JCOG0407	Primary	Nishina, 2016 (82)	Randomized phase ii study of second-line chemotherapy with the best available 5-fluorouracil regimen versus weekly administration of paclitaxel in far advanced gastric cancer with severe peritoneal metastases refractory to 5-fluorouracil-containing regimens (jcog0407)
CCOG0701	Primary	Nakanishi, 2016 (83)	Phase ii multi-institutional prospective randomized trial comparing s-1 plus paclitaxel with paclitaxel alone as second-line

Trial	Primary or secondary	Author, year	Title
			chemotherapy in s-1 pretreated gastric cancer (ccog0701)
SUN-CASE	**Primary**	**Moehler, 2016 (19)**	**Sunitinib added to folfiri versus folfiri in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled phase ii aio trial with serum biomarker program**
	Secondary	Nagel, 2018 (84)	Cytokeratin-18 fragments predict treatment response and overall survival in gastric cancer in a randomized controlled trial
T-ACT Study	Primary	Makiyama, 2020 (85)	Randomized, phase ii study of trastuzumab beyond progression in patients with her2-positive advanced gastric or gastroesophageal junction cancer: Wjog7112g (t-act study)
RADPAC	Primary	Lorenzen, 2020 (86)	Phase iii randomized, double-blind study of paclitaxel with and without everolimus in patients with advanced gastric or esophagogastric junction carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (radpac)
KCSG ST10-01	Primary	Lee, 2019 (87)	A phase iii study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer who failed in first-line therapy (kcsg st10-01)
DREAM	Primary	Kang, 2018 (88)	Efficacy and safety findings from dream: A phase iii study of dhp107 (oral paclitaxel) versus IV Paclitaxel in patients with advanced gastric cancer after failure of first-line chemotherapy
WJOG 4007	Primary	Hironaka, 2013 (89)	Randomized, open-label, phase iii study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: Wjog 4007 trial
Fushida 2016	Primary	Fushida, 2016 (90)	Paclitaxel plus valproic acid versus paclitaxel alone as second-or third-line therapy for advanced gastric cancer: A randomized phase ii trial
GOLD	Primary	Bang, 2017 (91)	Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (gold): A double-blind, randomised, placebo-controlled, phase 3 trial
Bang 2015	Primary	Bang, 2015 (92)	Randomized, double-blind phase ii trial with prospective classification by atm protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer
RAINBOW-Asia	Primary	Xu, 2021 (93)	Efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW-Asia): a randomised, multicentre, double-blind, phase 3 trial

Trial	Primary or secondary	Author, year	Title
	Secondary	CT.gov, 2017 (94)	A Study of Paclitaxel With or Without Ramucirumab (LY3009806) in Participants With Gastric or Gastroesophageal Cancer
NCT01579578	Primary	CT.gov, 2012 (95)	Assess the Efficacy of AZD8931 in Combination With Paclitaxel Versus Paclitaxel Alone in Patients With Gastric Cancer
Xiaoying 2019	Primary	Xiaoying, 2019 (96)	Comparison of efficacy and safety of second-line palliative chemotherapy with paclitaxel plus raltitrexed and paclitaxel alone in patients with metastatic gastric adenocarcinoma: A randomized phase ii trial
Wang 2021	Primary	Wang, 2021 (97)	Apatinib plus paclitaxel versus placebo plus paclitaxel as second-line therapy in patients with gastric cancer with peritoneal carcinomatosis: A double-blind, randomized phase ii trial
KEYNOTE-063	Primary	Chung, 2021 (98)	Pembrolizumab versus paclitaxel for previously treated advanced gastric or gastroesophageal junction cancer (KEYNOTE-063): A randomized, open-label, phase 3 trial in Asian patients
	Secondary	Cheol, 2020 (99)	Pembrolizumab vs paclitaxel as second-line treatment for asian patients with pd-l1-positive advanced gastric or gastroesophageal cancer (gc) in the phase iii keynote-063 trial
BRIGHTER	Primary	Shah, 2022 (100)	Randomized, Double-Blind, Placebo-Controlled Phase III Study of Paclitaxel +/- Napabucasin in Pretreated Advanced Gastric or Gastroesophageal Junction Adenocarcinoma
		NCT02178956, CT.gov, 2014 (101)	A Study of BBI608 Plus Weekly Paclitaxel to Treat Gastric and Gastro-Esophageal Junction Cancer
OGSG0701	Primary	Kawase, 2021 (102)	Randomized phase II study of Irinotecan-11 versus Paclitaxel versus each combination chemotherapy with S-1 for advanced gastric cancer that is refractory to S-1 or S-1 plus CDDP: OGSG0701

Single-arm trials for the relevant comparators have additionally been identified and are discussed in the response to A21.

Biliary cancer

Table 25 (corresponding to Table 36 in the Appendix of the company submission) presents the studies that meet the SLR eligibility criteria.

Table 25 List of publications included in the UK-specific SLR (biliary cancer)

Trial ID	Registry number	Publications	Study design	Publication type	Treatment
Single-arm trials					

Trial ID	Registry number	Publications	Study design	Publication type	Treatment
Hwang 2015	**NCT01127555**	**Hwang et al 2015 (103)**	**Phase II, open-label**	**Full-text**	**mFOLFOX3 (oxaliplatin + 5-fluorouracil + leucovorin)**
KEYNOTE-028	NCT02054806	Piha-Paul et al, 2020 (21); Yung-Jue et al, 2019	Phase Ib, open-label	Full-text	Pembrolizumab
KEYNOTE-158	NCT02628067	Piha-Paul et al, 2020 (21); Yung-Jue et al, 2019 (104); Marabelle et al, 2020 (4); Maio et al, 2022 (105)	Phase II, open-label	Full-text	Pembrolizumab
Kim 2019b	**NCT02350686**	**Kim et al 2019 (106)**	**Phase II, open-label**	**Full-text**	**XELOX (capecitabine + oxaliplatin)**
Sinn 2013	NCT00356161	Sinn et al 2013 (107)	Phase II, open-label	Full-text	Oxaliplatin + natrium folinate + 5-fluorouracil
RCTs					
ABC-06	NCT01926236; EudraCT, 2013-001812-30	Lamarca et al, 2021 (108), Lamarca et al, 2019 (109), Lamarca et al, 2022 (110)	Phase III, open-label	Full-text	Arm 1: ASC
					Arm 2: ASC + mFOLFOX (oxaliplatin + leucovorin + 5-fluorouracil)
Choi 2021	**NCT03464968**	**Choi et al, 2021 (111), Won et al, 2020 (112)**	**Phase II, open-label**	**Full-text**	**Arm 1: mFOLFOX (oxaliplatin + leucovorin + 5-fluorouracil)**
					Arm 2: mFOLFIRI (irinotecan + leucovorin + 5-fluorouracil)
NALIRICC	NCT03043547; EudraCT: 2016-003709-33	Vogel et al, 2022 (113)	Phase II, open-label	Conference abstract	Arm 1: nal-Irinotecan + 5- fluorouracil + leucovorin
					Arm 2: 5-flurouracil + leucovorin
NIFTY	NCT03524508	Yoo et al, 2021 (114), Changhoon et al, 2021 (115), Yoo et al, 2022 (116)	Phase IIb, open-label	Conference abstract/poster	Arm 1: Liposomal irinotecan + 5-fluorouracil + leucovorin

Two trials evaluating pembrolizumab have been identified, of which KEYNOTE-028 is a Phase 1b study investigating a not approved dosage of pembrolizumab (10mg/kg every two weeks) and is further discussed in the response to A30.

Choi et al. 2021, Hwang et al. 2015 and Kim et al. 2019 were used as the evidence source for FOLFOX, the relevant comparator in this appraisal for biliary cancer, as there was a sufficient clinical rationale for a class effect, meaning that UK clinical experts confirmed that they would not expect efficacy or safety outcomes to vary between individual regimens. Choi et al. 2021 also provided evidence on the efficacy of FOLFIRI, the other relevant comparator.

Further considerations led to the exclusion of the NALIRICC and NIFTY studies as relevant sources of efficacy evidence because the intervention in both studies includes liposomal irinotecan which is not approved (or used in clinical practice) in the UK for biliary cancer.
In Synn 2013, of the 37 patients enrolled only six had been previously treated with chemotherapy, the population relevant for this appraisal, with the remainder of the patients being previously treated instead with curatively intended surgery, biliary stenting, radiotherapy, afterloading and chemoembolization. As no outcome data specific for this subgroup were available, this study could not be used as a source of efficacy (PSM base-case or ITC/MAICs).

The ABC-06 study is a randomised controlled trial conducted in adult patients with advanced or metastatic biliary tract cancer who have progressed following first-line chemotherapy and were randomly assigned to active symptom control (ASC) and FOLFOX or ASC alone. Median (range) age in the FOLFOX + ASC arm is 65.0 (26.0, 84.0), with 53% of the patients being male and 68% patients with ECOG 1 (Table 26).

Table 26 Baseline characteristics of participants in FOLFOX studies (biliary cancer)

	FOLFOX + ASC (ABC-06), n=81	Pooled studies used in original ITC, n=139
Median (range) age	65.0 (26.0, 84.0)	62.5 (42.0; 80.0)
Male, n (%)	43 (53.0)	87 (62.6)
ECOG 1, n (%)	55 (68.0)	64 (46.0)

The addition of this study to the original pooling of FOLFOX studies carried out in the previous ITC (or PSM base-case) results in a slight improving of median PFS and similar results for median OS, compared to previous pooling (Table 27). The updated results should be treated with caution as the intervention in the ABC-06 study also included ASC which entailed early identification and management of biliary tract and cancer-related complications and symptom management arising from tumour progression, which may not be consistent with other evidence.

The KM plots provided below compare the pooled results from the three comparator studies previously used in the ITC of pembrolizumab vs FOLFOX with the pooled results from the totality of studies (n=4) identified for FOLFOX, for PFS and OS (Figures Figure ***5***Figure ***6***). No substantial differences can be observed in the shape of the curves (black lines) by visual inspection; it should be noted that there is an offset from the origin in the original pooled study KMs (from Appendix P) and this should be considered in interpretation. Broadly, the landmark proportions are virtually identical which is corroborated by the medians – refitting PSMs is unlikely to make a great deal of difference to results.

Table 27 PFS and OS pooled analysis for FOLFOX (biliary cancer)

	Pooled studies used in original ITC, n=139	**ABC-06 study added to previously pooled studies**
Median PFS, months	2.7 (95% CI 1.9, 3.3)	3.2
Median OS, months	6.5 (95% CI 5.1, 8.0)	6.3

Figure 5 PFS KM plot for FOLFOX - original ITC (left) vs pooled studies (right)

Figure 6 OS KM plot for FOLFOX - original ITC (left) vs pooled studies (right)

Colorectal cancer

Table 45 in the Appendix of the company submission presents the studies that meet the SLR eligibility criteria.

Four trials evaluating pembrolizumab have also been identified, of which KEYNOTE-028 and Le et al. 2015 are discussed in the responses to A30 and A31, whereas Michalaki 2020 study relevance to this appraisal was discussed in section D.1.5.6.1 of the company submission Appendix.

Based on current understanding of the clinical practice in the UK following clinical expert consultation, 14 comparator studies (RCTs) corresponding to 34 publications evaluated interventions relevant to this appraisal (Table 28).

Three studies (RECOURSE, TERRA and Yoshino et al. 2012) evaluated the efficacy of TAS-102 (trifluridine/tipiracil) and all of these were selected as sources to inform the efficacy of this comparator. Of the eleven studies on FOLFOX and/or FOLFIRI, five were used in the ITC (Li et al. 2018, ECOG 3200, Cao et al. 2015, Moore et al. 2016 and Xie et al. 2014).

The remaining six studies (BEYOND, CAPRI-GOIM, Liu et al. 2015, Peeters et al. 2010, RAISE and VELOUR) when pooled together with the previously used studies show marginal difference in PFS and OS compared to the studies previously used in the ITC (

Table ***29***). PFS and OS results from each study are provided in Table 30.

Table 28: List of included trials in UK-specific SLR for relevant interventions (colorectal cancer)

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
Studies on pembrolizumab (single-arm trials)				
KEYNOTE-028	NCT02054806	O'Neil 2017 (22)	Safety and antitumor activity of the anti-pd-1 antibody pembrolizumab in patients with advanced colorectal carcinoma	--
KEYNOTE-164	NCT02460198	Le et al. 2020 (117)	Phase ii open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: Keynote-164	Diaz et al., 2020 (118), Le et al. 2021 (119)
Le 2015	NCT01876511	Le et al. 2015 (120)	PD-1 Blockade in Tumors with Mismatch-Repair Deficiency	--
Michalaki 2020	--	Michalaki 2020 (121)	Safety and efficacy of pembrolizumab monotherapy in patients with advanced colorectal msi-h/dmmr cancers	--
Non-pembrolizumab studies (RCTs)				
BEYOND	EudraCT 2017-004519-3 8	Aparicio et al., 2022 (122)	Randomized phase II trial of FOLFIRI-panitumumab compared with FOLFIRI alone in patients with RAS wild-type circulating tumor DNA metastatic colorectal cancer	--

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
			beyond progression to first-line FOLFOX-panitumumab: the BEYOND study (GEMCAD 17-01)	
Cao 2015	**--**	**Cao et al., 2015 (123)**	**A multi-center randomized phase ii clinical study of bevacizumab plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for Chinese patients with metastatic colorectal cancer**	**--**
CAPRI-GOIM	EudraCT 2009-014041-81	Ciardiello et al., 2016 (124)	Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): A randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX	--
ECOG 3200	**--**	**Giantonio et al., 2007 (125)**	**Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group study E3200**	**Reddy et al., 2005 (126)**
Li 2018	**NCT01661270**	**Li et al., 2018 (127)**	**Aflibercept plus FOLFIRI in Asian patients with pretreated metastatic colorectal cancer: A randomized phase iii study**	**--**
Liu 2015	--	Liu et al., 2015 (128)	A randomized phase ii clinical study of combining panitumumab and bevacizumab, plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for patients with metastatic colorectal cancer and KRAS mutation	--
Moore 2016	**NCT01111604**	**Moore et al., 2016 (129)**	**Randomized phase II study of modified FOLFOX-6 in combination with ramucirumab or icrucumab as second-line therapy in patients with metastatic colorectal cancer after disease progression on first-line irinotecan-based therapy**	**--**

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
Peeters 2010	NCT00339183	Peeters et al., 2010 (130)	Randomized phase iii study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer	Bennet et al., 2011 (131), Peeters et al., 2014 (132), Peeters et al., 2015 (133)
RAISE	NCT01183780	Tabernero et al., 2015 (134)	Ramucirumab versus placebo in combination with secondline FOLFIRI in patients with metastatic colorectal cancer that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study	Cohn et al., 2017 (135), Lim et al., 2019 (136), Obermannova et al., 2016 (137), Tabernero et al., 2018 (138), Yoshino et al., 2017 (139), Yoshino et al., 2019 (140)
RECOURSE	**NCT01607957**	**Mayer et al., 2015 (141)**	**Randomized trial of tas-102 for refractory metastatic colorectal cancer**	**Longo-Munoz et al., 2017 (142), Van Cutsem et al., 2017 (143), Van Cutsem et al., 2018 (144)**
TERRA	**NCT01955837**	**Xu et al., 2018 (145)**	**Results of a randomized, double-blind, placebo-controlled, phase iii trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: The TERRA study**	**--**
VELOUR	NCT00561470	Van Cutsem et al., 2012 (146)	Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen	Chau et al., 2014 (147), Joulain et al., 2013 (148), Ruff et al., 2015 (149), Ruff et al., 2018 (150), Tabernero et al., 2014 (151), Van Cutsem et al., 2016 (152), Van Cutsem et al., 2020 (153)

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
Xie 2014	--	Xie et al., 2014 (154)	Safety and efficacy of second-line treatment with folinic acid, 5-fluorouracil and irinotecan (FOLFIRI) in combination of panitumumab and bevacizumab for patients with metastatic colorectal cancer	--
Yoshino 2012	JapicCTI-090880	Yoshino et al., 2012 (155)	TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial	--

Table 29 PFS and OS pooled analysis for FOLFOX/FOLFIRI (colorectal cancer)

	Pooled studies in original ITC, n=681	Additional six studies added to previously pooled studies, n=2,534
Median PFS, months	4.9 (95% CI 4.3, 5.4)	4.8
Median OS, months	11.8 (95% CI 10.7, 12.6)	11.9

Table 30 PFS and OS analysis for FOLFOX/FOLFIRI (colorectal cancer - additional six studies)

Trial ID	Treatment	Population	N	Median OS months (95% CI)	Median PFS months (95% CI)	KMs available
BEYOND	FOLFIRI	CRC	13	10 (3-15)	4 (2-8)	Yes
CAPRI-GOIM	FOLFOX	CRC, KRAS exon 2 wild type	79	14 (12.9-15.1)	4.5 (3.3-5.7)	Yes
Liu et al.2015	FOLFIRI	CRC, KRAS wild type	35	11 (8.2-15.4)	3.8 (3-6.7)	Yes
	FOLFIRI	CRC, KRAS mutant	34	10.5 (6.1-15.3)	4.1 (2.5-8.4)	Yes
Peeters et al. 2010	FOLFIRI	CRC, KRAS wild type	294	12.5	4.9 (3.8-5.5)	Yes
	FOLFIRI	CRC, KRAS mutant	248	11.1	5.4 (4-5.6)	Yes
	FOLFIRI	CRC, RAS wild type	213	13.9 (11.9-16)	4.6 (3.7-5.6)	No
	FOLFIRI	CRC, RAS mutant	294	11.1 (10.2-12.4)	4 (3.6-5.5)	No
RAISE	FOLFIRI	CRC	536	11.7 (10.8-12.7)	4.5 (4.2-5.4)	Yes
VELOUR	FOLFIRI	CRC	614	12.06 (11.1-13.1)	4.67 (4.2-5.4)	Yes

The KM plots provided below compare the pooled results from the five comparator studies previously used in the ITC of pembrolizumab vs FOLFOX/FOLFIRI with the pooled results from the totality of studies (n=11) identified for FOLFOX/FOLFIRI, for PFS and OS (FiguresFigure ***7***Figure ***8***). No substantial differences can be observed in the shape of the curve (black lines) by visual inspection and again (taking account of the offset) the landmark proportions are virtually identical between the KM plots and this is corroborated by the calculated medians. Fitting updated PSMs is unlikely to make any difference to results.

Figure 7 PFS KM plot for FOLFOX/FOLFIRI - original ITC (left) vs pooled studies (right)

Figure 8 OS KM plot for FOLFOX/FOLFIRI - original ITC (left) vs pooled studies (right)

Conclusions

In summary, there is some uncertainty that the ABC-06 study should be pooled with the other FOLFOX studies (biliary cancer). Furthermore, in either this case or the six additional studies for FOLFOX/FOLFIRI (CRC), visual inspection and calculated summary statistics show that the additional pooling is unlikely to have a significant impact on fitted PSM comparator curves and, given the wider context of significantly better OS/PFS outcomes for pembrolizumab versus these chemotherapy comparators, there is unlikely to be a significant impact on cost-effectiveness results. Any theorised impact is unlikely to be any greater than picking an alternative parametric function for these comparators (that already have mature KMs) in the submitted base-case model.

A 45. Priority question: As the pembrolizumab data were derived from single arm studies, ITC methods were used to estimate the effects of pembrolizumab relative to relevant comparators. Unadjusted ITC methods were used for most of the evidence, whilst adjusted methods (MAIC) were used for endometrial cancer data.

a) Please explain why a MAIC was used only for one population and not the others. Please conduct a MAIC for all cancer subgroups.

b) **Other methods of population adjustment are available e.g. simulated treatment comparison (STC). Please refer to NICE technical support document (TSD) 18 in considering other methods.**

c) **For endometrial cancer, it appears that the company's own trial (KEYNOTE-775) was used. Please explain why population adjustment was used instead of an individual patient data method of adjustment, as described in NICE TSD 17. Where individual participants data (IPD) are available for the comparator, please conduct an analysis, providing a full assessment of validity such as the QuEENS checklist, following the recommendations of TSD 17.**

d) **Please explain the criteria for the 'most clinically plausible extrapolation'.**

e) **It is difficult to find the tabulated effects derived from the parametric survival distributions approach in the company documents. Please highlight the location of these results or make these results available.**

MAIC vs ITC

The rationale for conducting ITCs or MAICs is explained in B.2.9 and the justification for not using them in the base-case to model comparator efficacy is also presented in that section as well as B3; in the latter case the underlying data for pembrolizumab and comparators in each case did not support methods that made strong assumptions about constant treatment effects and so independent parametric curves were used to model comparator efficacy in the base-case.

The decision to conduct MAICs over ITCs was based on a balance between impact on effective sample size; likely impact of treatment effect when adjusting vs. not adjusting; and availability of data to allow weighting on chosen variables.

The more variables for weighting and related number of covariates can mean a MAIC cannot be run or that the effective sample size after weighting is very small. The sample sizes within the gastric tumour type (n=51), small intestine (n=27), and cholangiocarcinoma (n=20) are likely too small to support MAIC analyses. To illustrate, the weighting based on 5 variables listed in B.2.9 reduced the sample size

by 58% in the endometrial MAIC (vs. TPC). In addition, the impact was relatively minimal in endometrial, and this may be because the TPC source is from a MSI-H/dMMR selected source.

The relevant five variables for weighting were not always available; for example in small intestine Overman et al. 2018 did not contain adequate histology information or line status in the relevant form; in gastric (FOLFIRI comparison) Moehler et al. 2016 did not report performance status by ECOG. In a similar way unadjusted ITC methods were chosen for CRC because many of the sources used for KM pooling (i.e. chosen to reflect comparator efficacy) did not have the relevant weighting variables. For example, Moore et al. 2016, a source for FOLFIRI efficacy, did not report an adequate breakdown of previous lines of treatment.

KEYNOTE-775 IPD availability

The KEYNOTE-775 trial was conducted as part of an alliance with both Merck and Eisai as the sponsors and data owners. The KEYNOTE-158 submission is outside of this alliance and MSD does not have the authority to use individual patient data from the KEYNOTE-775 trial to support submissions outside of the alliance. Therefore, only publicly available data from KEYNOTE-775 were digitized and used to support the KEYNOTE-158 submission.

STC

There are several reasons fitting regression based STC models would likely make marginal impact on results (and the appraisal in general):

- Many of the reasons MAICs are not used in the base-case apply to STC regression-based approaches. Any regression-based method used to derive a treatment effect in the form of a HR will require similar proportional hazards assumptions for use in modelling.
- The same or similar set of summary statistics would be required from comparator studies as with a MAIC.
- STC regression methods will likely also be limited by sample size considerations: regression models applied to tumour site IPD, in proportion to

the number of variables included in models (and distribution of these in the IPD), will reduce the effective sample size in an analogous way.

"Tabulated effects"

It's not clear what is meant here or if this refers to the parametric BHM base-case or standard parametric models. Appendix J includes "raw" hazard plots overlayed with hazards from parametric models. If this question refers to landmark proportions, these are automatically calculated from the model at 1,2, 3, 10 and 15 years when new parametric models are selected (e.g., BHM, standard PSM, BHM piecewise for PFS and specific functions) and deterministic model re-run (see "Summary KM" and "summary outcomes" tables in PFS and OS sheets for this).

Adverse events

A 46. Priority question: Following separate modelling for each tumour site, populations are aggregated to generate outcomes across all tumour sites. The EAG is questioning the appropriateness of aggregating results, as there is substantial heterogeneity between patient populations.

Please justify why aggregating results across tumour sites was deemed appropriate in the economic model as opposed to modelling all tumour sites individually.

The term "aggregation" can mean a number of things in this appraisal, the following separate issues are discussed in full in the subsequent modelling question responses (section B):

- Degree of heterogeneity in pembrolizumab efficacy outcomes (PFS and OS) and relevant methodology that makes different assumptions about this (i.e. BHM vs individual parametric fits for pembrolizumab efficacy)
- Rationale for how modelling results are presented in terms of weighting final results (i.e. weighting model outcomes such as total QALYs, incremental results and ICERs):
    - Individual pairwise comparisons with individual comparators within a tumour site and these can be ascertained from the model (and are presented in appendices of the submission)

- Weighting of comparator results within a tumour site based on clinician elicited market share proportion estimates. See Table 72 in document B for weightings. There is some confusion here probably because this is in the costing section of B3, however it is best to think of these weightings as applying to piecewise comparisons (and building up from there).

- Overall weighting of model results across the multi-tumour basket trials based on trial proportions in the base-case and epidemiological calculations in scenario analyses (calculating back from patient prevalence based on line, MSI-H/dMMR status etc to produce tumour distribution across all MSI-H/dMMR patients). See Table 43 in document B for tumour site distribution.

In terms of adverse events, there was no "aggregation" or assumption of homogenous adverse event rates across tumour sites (See B..3.3.10): incidence for pembrolizumab were taken from the relevant tumour site (and associated KEYNOTE-158 and KEYNOTE-164 trial) and for comparators from literature and previous appraisals relevant to each tumour site. Broadly, as discussed in section B1 these AEs were in line with what is expected from treatment with an immunotherapy.

Section B Clarification on cost-effectiveness data

Model structure

B 1. Priority question: Following separate modelling for each tumour site, populations are aggregated to generate outcomes across all tumour sites. The EAG is questioning the appropriateness of aggregating results, as there is substantial heterogeneity between patient populations.

Please justify why aggregating results across tumour sites was deemed appropriate in the economic model as opposed to modelling all tumour sites individually.

Individual pairwise comparisons are accessible from the model (and presented in the appendix), results by tumour site are also presented in Document B. It is highly

plausible that MSI-H/dMMR status is a significant “driver” of efficacy outcomes (see response to A1 41) and so there is a case for considering a multi-cohort structure that captures both cohort specific results but also provides results that reflect the overall population covered in the license indication. See further responses below and the response to the question above.

B 2. Priority question: The NICE Decision Support Unit (DSU) TSD 19 recommended the use of state transition models (STMs) alongside partitioned survival models (PSMs) to verify the plausibility of PSM extrapolations and to explore key clinical uncertainties in the extrapolation period.

a) **Please justify the use of a partitioned survival approach given the issues highlighted in NICE DSU TSD 19 and given that, for tumour sites included in KEYNOTE-158, the time-to-death utility modelling approach is not in line with the utilised model structure (i.e., there seems to be a mismatch between the chosen model structure and the chosen approach to estimate HRQoL).**

b) **Please use state transition modelling to assist in in verifying the plausibility of the PSM extrapolations and to address uncertainty in the extrapolation period (NICE DSU TSD 19, recommendation 11).**

TSD 19 recommends that assumptions behind each method should be clearly stated. It makes clear that the “choice of modelling approach may be constrained by the available evidence.” TSD19 notes the two key downsides of the PartSA approach:

- Transitions to states are modelled in an independent fashion and there can be an implicit assumption of no structural relationship between the transition to states
- Extrapolated periods are strongly related to the within-trial period: “trends in the hazard of each endpoint and treatment effects on these hazards observed within the trial period are assumed to generalise to the extrapolation period”.

With the available data for pembrolizumab and the comparators, there is no strong case that a STM approach would mitigate the two downsides listed above.

Firstly, this is because the data requirements for a STM could not be met and so the differences in approach would be superficial in practice. OS and PFS are modelled independently of each other, but are accounted for in this therapy area in that PFS also accounts for death events. There is no evidence that patients routinely (or at all) move backwards from progressed to a progression free health state and so this structural feature is consistent with the disease areas. There are also minimal subsequent lines of therapy at the modelled stage of the treatment pathway and this is a further reason why this approach is not thought to be a significant limitation.

Given the 1-arm nature of the pivotal trials and the comparator sources explored there would be no difference in uncertainty relating to extrapolations. There is also no individual patient level data for the comparators, and this would also limit exploration of more complex STMs (i.e. that could potentially produce divergent cost-effectiveness results). In particular, it would be hard to find data for the PPS to death transition that would have to be explicitly modelled here.

Secondly, the submission and the responses to these clarification questions has provided the information/scenarios recommended in TSD19 to explore the two downsides listed above. In particular, standard curve selection methods (e.g., fit statistics and plots to measure PH assumptions and general hazard plots etc) applied were consistent with NICE recommended methods. It is not common to submit two model types in oncology appraisals.

Population

B 3. Priority Question: Analyses of pembrolizumab survival outcomes were conducted using the ASaT populations of KEYNOTE-158 and KEYNOTE-164. The intention-to-treat (ITT) population is more commonly used to analyse survival outcomes as it provides a more realistic representation of the population that would be treated in practice, including patients who may not have dropped out of the study or not adhered to the treatment protocol. It is unclear whether ASaT or ITT populations were used to assess comparator survival outcomes.

a) **Please provide an explanation as to why the ASaT populations of KEYNOTE-158 and KEYNOTE-164 were selected over the ITT populations in the analyses of pembrolizumab survival outcomes and discuss how this could potentially bias the outcomes of the analysis.**

b) **Please provide clarification regarding whether the ASaT population or ITT population was used to assess the survival outcomes of treatment comparators.**

c) **Please provide a scenario analysis and updated economic model, utilising the ITT population for both pembrolizumab and comparators to assess survival outcomes.**

Please see the response to question A38.

Intervention and comparators

B 4. Priority question: The comparators included in the economic evaluation were not in line with those outlined in the final scope and were applied as a basket of treatments to reflect standard of care (SoC). An overview of comparators that were included in the final scope, as well as those considered by the company is shown in Table 1 of the CS.

a) **Please provide detail regarding the appropriateness for each excluded comparator that was mentioned in the NICE scope and provide evidence to support why it was deemed appropriate to deviate from the final scope for each tumour site.**

b) **Please provide justification for using treatment baskets as the comparator (i.e., does this reflect UK clinical practice for each tumour site, in the respective populations and in terms of the effectiveness of usual care?).**

c) **Please clarify whether equal effectiveness was assumed for the individual treatments included in the comparator basket. If so, please provide justification for this assumption and elaborate on how this could potentially bias the results of the analysis.**

d) **Per individual tumour site, please provide the results of a fully incremental analysis and updated economic model with all comparators listed in the final scope.**

e) **Nab-paclitaxel was utilised as a proxy chemotherapy for FOLFIRI/FOLFOX in small intestine cancer. No justification is provided in Section B.3.2.3.2 of the CS. Please provide justification, supported by empirical evidence, if available, for the appropriateness of using nab-paclitaxel as a proxy chemotherapy (i.e., how similar are these in terms of effectiveness and costs).**

f) **Table 1 of the CS suggests that, for people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer, carboplatin was considered by the company, in addition to paclitaxel and doxorubicin. In Section B of the CS and the economic model however, the company only considers paclitaxel and doxorubicin as treatment comparators for endometrial cancer. Please justify why carboplatin was not a modelled treatment comparator for endometrial cancer.**

Response to a

Exclusions of comparators stated in the NICE scope are justified based on clinical opinion but also consensus from previous appraisals in the relevant tumour site.

CRC

The rationale for excluding nivolumab and ipilimumab can be found in response to A18. Single-agent irinotecan and raltitrexed are not considered relevant comparators in this appraisal as clinical expert opinion confirmed that they are not routinely used in clinical practice unless other treatments are contraindicated. This is well established and supported by opinion from TA716 (see ACM slides and AEG report).

The list of comparators includes a pooled group of three regimens: FOLFIRI (folinic acid, fluorouracil and irinotecan), FOLFOX4 and FOLFOX6 (two different regimens of folinic acid, fluorouracil and oxaliplatin). This group is referred to as pooled FOLFOX/FOLFIRI. The pooled comparator was chosen for the CRC tumour site to maximize as much of the relevant data as possible. Grouping of different

comparators was only permitted where there was sufficient clinical rationale for a class effect based on clinical opinion and previous appraisal precedent. In particular, the FAD for TA709 concluded “Clinical experts explained that FOLFOX, FOLFIRI and CAPOX treatments are interchangeable and, although each have different advantages and disadvantages, they can be considered equivalent.”. This is supported by previous appraisals whereby variants of FOLFOX, FOLFIRI have been pooled or assumed to be equivalent efficacy, such as TA439.

Multiple relevant studies were identified for TAS-102 and so these were pooled before an ITC was performed (or parametric curves fit, as in the base-case analysis). The pooling process is fully explained in the specific appendices related to ITCs (Appendix P).

Endometrial

Based on clinical expert consultation and published guidelines, standard of care is chemotherapy such as paclitaxel, doxorubicin and carboplatin. The chemotherapy arm (physician’s choice of paclitaxel or doxorubicin) from KEYNOTE-775 was used to inform efficacy for these chemotherapies as there was clinical consensus that efficacy will not vary significantly between these. This is also supported by ongoing appraisal ID3811 that also listed “Chemotherapy (such as paclitaxel, carboplatin, doxorubicin)” as a comparator but there was consensus that the TPC arm of KEYNOTE-775 broadly reflects the efficacy for these chemotherapies. The support for KEYNOTE-775 as reflective of these is also seen in TA779 where this was the preferred source of data for this specific comparator grouping.

Hormone therapy is only used with palliative intent if all other treatment options are exhausted, or patients cannot tolerate further lines of chemotherapy. This positioning was also supported by consensus in the ongoing appraisal ID3811 and no comparison was made with hormone therapies (despite it being in the NICE scope).

Gastric, small intestine, and biliary cancer

Established clinical management without pembrolizumab has been identified based on European guidelines and clinical expert consultation.

Again, if significantly relevant multiple studies were identified for the same regimen, these are usually pooled and this is fully explained in the specific appendices related to ITCs (Appendix P). This pooling is summarised in Table 29 of Document B: FOLFIRI in Gastric and mFOLFOX in Biliary.

With regard to small intestine cancer, clinical experts identified FOLFOX/FOLFIRI as the treatment of choice but did not expect MSD to find any published evidence on efficacy. This was confirmed in the systematic literature review which only identified evidence for nab-paclitaxel, which is used in the cost-effectiveness analysis (see response to question e below). Clinical consensus was that this would be a reasonable proxy, given the lack of other efficacy data.

Response b to f

Sources of efficacy for comparators within a tumour site are chosen based on published guidelines and validated by clinicians, but also reflect the published data that is available for a comparator treatment: Table 1 (Document B) describes any divergences from the published scope and Table 29 summarises the sources for comparator efficacy that are used in the base-case model approach (i.e. independently fit parametric curves) - it is important to note that the ITCs also used these sources, but the ITCs were not used to inform comparator efficacy in the base-case for the reasons described in the submission.

Each comparison versus a treatment reflects a treatment that constitutes standard of care in the UK. Weighting (or “aggregation”) at the tumour site level (when multiple comparators) or overall across tumour sites only occurs at final model results stage (i.e. weighting of total QALYs, costs and other final model outputs).

It is not the case that any assumptions regarding efficacy were made for comparator treatments. It is best to think of different methods and relations between them as summarised in Table 44 and Table 45 of document B. The BHM is used in the base-case to model and extrapolate absolute pembrolizumab OS/PFS (but the alternative parametric fits are also programmed in the model and provided in scenario analyses). Independent parametric fits are then applied to comparator sources in the base-case to extrapolate OS/PFS (but ITC/MAICs are programmed into the model). The model produces conventional model outputs for each pairwise comparison and

only the final model outcomes are then weighted – the model can produce comparisons and associated results for each individual pairwise comparison.

Please see the responses to B4a and A18. Fully incremental analyses by tumour site can be produced by the model (Results table sheet) and this is automatically plotted on a cost-effectiveness frontier. However, given this is not a multiple technology appraisal and the focus is on the relative cost-effectiveness of pembrolizumab vs standard of care, it does not seem appropriate to provide fully incremental results.

As summarised in Table 74 of document B, nab-paclitaxel was costed as FOLFOX so as to more appropriately reflect costs consistent with the clinician identified comparator (FOLFOX/FOLFIRI). This was the only identified evidence, however clinicians suggested nab-paclitaxel is not an unreasonable proxy given the similarity in PFS/OS outcomes across standard-of-care chemotherapies in the different tumour sites: by 5 years the KMs consistently show that most patients are dead and accrued model LYs and QALYs for all individual comparators are not too dissimilar (i.e. cluster around 1). There is some evidence from the sources for other tumour sites, that this may be a reasonable (and potentially conservative) proxy for FOLFOX/FOLFIRI: within the gastric site, for example, the evidence suggests that paclitaxel may be a bit more efficacious than FOLFIRI. This can be seen visually from the KMs but is also indicated by the ITCs that were explored (Table 30 of Document B).

In relation to carboplatin in endometrial, please see the response to B4a.

B 5. Priority question: The SoC arm in the economic model was applied as a basket of comparators that varied between the different indications. Costs of the SoC arm per indication were weighted based on available market share data within each tumour site, as shown in Table 72 of the CS. However, it is unclear whether and how these market share data were used in the effectiveness estimates (survival analysis) of the SoC arm. It appears as though the company simply used whichever comparator evidence was available, sometimes only using a single comparator, sometimes using a pooled comparator (without weighting).

a) **Per indication, please provide a tabular overview of how the effectiveness estimates of the different comparators were combined/weighted/pooled to inform survival analyses of the SoC arm, for each tumour site separately and indicating the source of evidence for each comparator per tumour site.**

b) **Please justify the differences between the approaches of weighting costs and effects to inform the SoC arm and elaborate on the plausibility and potential implications of using different approaches to weigh costs and effects.**

A tabular overview of the comparators considered within the economic model by tumour site, as well as their market share and data sources are provided below, combining evidence presented in the CS in Table 29 and Table 72.

Table 31 Combined information on source and market share within tumour site

Tumour site	Comparator 1	Comparator 2
CRC	TAS-102	Pooled FOLFOX/FOLFIRI
Market share	30%	70%
Source	Yoshino et al. 2012 Mayer et al.2015 Xu et al. 2018	Li et al. 2018 Giantonio et al. 2007 Cao et al. 2015 Moore et al. 2016 Xie et al. 2014
Endometrial	Paclitaxel	Doxorubicin
Market share	33.3%	66.7%
Source	Makker et al. 2022	Makker et al. 2022
Gastric	Paclitaxel	FOLFIRI
Market share	70%	30%
Source	Chao et al. 2021	Moehler et al. 2016 Sym et al.2013
Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	
Market share	100%	
Source	Overman et al.2018	
Cholangiocarcinoma	mFOLFOX	mFOLFIRI
Market share	90%	10%
Source	Choi et al.2021 Hwang et al. 2015 Kim et al. 2019	Choi et al. 2021

Abbreviations: CRC, colorectal cancer; FOLFIRI, folinic acid, fluorouracil and irinotecan; mFOLFOX, modified folinic acid, fluorouracil and oxaliplatin

There is no difference in how cost and health outcomes are weighted to generate the SoC results within each tumour site. The model evaluates each comparator separately, generating aggregate and disaggregated results, before results are weighted by the respective market shares. For deterministic analysis, detailed calculations for how this is done can be found in the economic model on the Results Tables Sheet (AJ29:AN262). To estimate cost-effectiveness results for the overall indication, tumour site specific results are then weighted based on the expected distribution of patients across each of the relevant tumour sites. Calculations deriving the overall indication results for the SoC arm can be found on the Results Tables Sheet (AP29:AP262).

Effectiveness

B 6. Priority question: According to the CS, to ensure heterogeneity was captured in the survival modelling, Bayesian hierarchical models (BHMs) were used to model OS and PFS for pembrolizumab. These models assume that outcomes are similar across tumour sites but allow for tumour-site-dependent parameters to capture observed heterogeneity. Piecewise BHM was also explored for the modelling of PFS to account for the poor fit of the one-piece distributions to the observed Kaplan–Meier (KM) function between 0 and 10 weeks.

a) **Please provide comprehensive references and literature regarding the methodology and application of BHM.**

b) **Please provide a further detailed justification for the assumptions underlying the BHMs, e.g. assuming similarity of outcomes, or efficacy of the intervention, across different tumour sites, especially given that hazard rates are likely to vary considerably for the different tumour sites.**

c) **Please elaborate on the plausibility of using the BHM approach for the modelling of pembrolizumab OS and PFS, especially considering the poor visual fit of the curves to the KM data.**

d) **Please justify why the BHM approach was not applied to the comparators in the cost effectiveness analysis.**

e) **In line with the comparator arm, please provide an updated economic model and scenario analyses modelling pembrolizumab OS and PFS using standard parametric models, and justify the curve choices based on guidance from NICE DSU TSD 14 and 21 on (flexible methods for) survival analyses.**

f) **Regarding the piecewise models, please clarify how many events occurred before and after the cut-point and how many patients were at risk at the cut-point.**

g) **Please justify the plausibility of the (extrapolation) approach used for the estimated piecewise models, given the number of patients at risk and observed events (both per treatment) to estimate the tail.**

h) **Please justify the selected cut-point given the responses above and provide an updated economic model as well as scenario analyses assuming different cut-points.**

Methodology and rationale of BHM (a and b)

We refer the EAG to section B.3.3.3.1 of Document B for detail on the rationale for this approach and to Appendix O for further detail on the survival functions and which fixed effect covariates or how random effects terms are applied. We also refer the EAG to the sources referenced in the relevant B3 section including the HTA report for modelling approaches for histology independent medicines and the NTRK appraisals.

To summarise, the key rationale for exploring this methodology are as follows:

- BHMs assume that outcomes, or the efficacy of the intervention, differ by tumour site but are also part of an overall group that has similarities that drive efficacy (i.e. MSI-H/dMMR is a significant driver), and the different tumour sites do not determine a particular ordering of effectiveness a priori (i.e. the tumour sites are exchangeable).
    - This is a middle-ground between assuming total homogeneity (pooling all tumour cohorts) and treating them as independent trials.

- BHMs capture heterogeneity between tumour sites and allow information to be borrowed between groups or ‘baskets’ through the use of shared random effect parameters. This method aims to increase the precision of estimates when compared to analysing individual baskets separately, while also reducing the chances of obtaining implausible estimates for tumour sites represented by few patients.
    - This can also mean that smaller sites (i.e., tumour sites where sample sizes are smaller) can borrow information from larger sites.

The BHM framework in this context can also be seen as combining methods used in appraisals and applied medical statistics on a regular basis: Bayesian survival analyses (Soikkeli et al, 2019) (156); survival models using covariates (i.e. that act on survival model parameters); and multilevel modelling frameworks such as mixed-effects models for utility analyses or cluster trial analyses (i.e. the random effect/clusters are per trial site whereas here they are by tumour/cancer type).

A BHM allows variation in hazards by tumour type, as shown in the derivation in Appendix O. For a given survival function, the rate/scale/location parameter is a function of various fixed effects and random effects, the latter of which allow variation by tumour site (i.e., intercept of the model varies by tumour site) and this in turn will impact the estimated hazard for each tumour site.

As explained in B.3.3.3.1.1, it should be noted that the Bayesian modelling approach has been implemented in a way consistent with the model specified by the York ERG in the report for the Entrectinib appraisal: “Heterogeneity in time to event outcomes (PFS, OS) can be explored using the BHM in a similar way. The model assumes a common parametric distribution for each tumour type, but with a different location parameter. Information on this parameter can be borrowed across the different tumours, according to an estimated heterogeneity parameter. The results from this type of model would be different distributions of PFS or OS for each tumour type which could be incorporated in the economic model”.

The term related to heterogeneity can be seen as the hyperparameter (sigma_gamma) described in Appendix O and can be interpreted as indicating the degree of heterogeneity produced by these random effects (i.e., standard deviation

of the random effect terms) and the estimated mean (and distribution) will vary by the BHM parametric function that is run. As described, the line and distribution plots of posterior distributions should be interpreted with caution. All plots indicate a narrow posterior distribution for this hyperparameter (i.e., it is relatively certain and well defined). The hyperparameter for the base-case selected BHM function for PFS/OS (log-normal) which was selected based on model fit and clinical validation indicates slightly less heterogeneity than the other functions.

More general information about BHMs in the context of the NTRK appraisals is contained in the response to B29 below.

Visual fit of BHMs and rationale of piecewise (c)

OS BHM models have a reasonable fit but depending on the function selected they tend to cut the “tail” at different points (see Figure 17 in Document B). PFS BHM functions tend to sometimes overestimate the drop up to 10 weeks but then consistently underestimate the tails (see Figure 29 in Document B). Standard parametric distributions used within the Bayesian hierarchical modelling framework applied in the base case were not sufficiently flexible to suitably capture the change in hazard function. This meant extrapolated curves were overly informed by this sharp decline at 9 weeks and failed to capture the subsequent decrease in the pembrolizumab PFS hazard function.

This initial fitting to the drop is likely related to the fact the first on-study imaging time point was performed at 9 weeks in both KEYNOTE-164 and KEYNOTE-158. Independent parametric fits (when this is selected in the model and viewed in the OS and PFS sheet) also struggle to fit this drop and so it is not a feature of BHMs.

A piecewise BHM model was also explored for PFS outcomes only to account for the poor fit of the one-piece distributions to the observed Kaplan–Meier function between 0 and 10 weeks. This is programmed into the model but also presented in appendix J.2.1.2 and these produce overall better fits in PFS.

In document B the fit statistics (DIC) of base-case BHM (“single piece”) models have been considered in curve selection (i.e., observed period of fittings) and in addition clinical validation was undertaken at the advisory board: all BHM functions/curves

overlaying KMs by tumour site were presented (with landmark proportions) and a consensus opinion achieved on selection in terms of long-term extrapolations. An example of a slide is given below:

BHM for comparators (d)

This analysis, to model absolute OS/PFS of comparators via a BHM is not possible for a number of reasons:

- The same treatment is not used in each of the tumour sites and there is no single basket trial reflecting the comparator efficacy
- Sources are disparate (given the literature) and very few reflect MSI-H/dMMR status and so there is no reason to assume some relationship between different sites
- There is no IPD available for comparator sources

Independent (standard) parametric fits (e)

These are explored in scenario analyses and fully implemented in the model and user selectable. By clicking the button to add a new scenario in the Model controls sheet you can also select “Scenario - naïve PSMs”, which chooses the selections preferred by MSD based on fit statistics etc. The table below gives a general rationale for the PFS/OS function selections for pembrolizumab in this scenario

based on fit statistics, clinical plausibility in terms of relationships between PFS and OS and plausibility of long-term extrapolations.

Table 32 Justification for chosen parametric curves in PSM scenario

	Best AIC	Best BIC	Selection in scenario	Notes for selection
CRC				
OS	Gompertz	Gompertz	Weibull	All very close statistical fit except exp and log-logistic. From CRC previously untreated pembrolizumab trial (KEYNOTE-177) showed 45% alive at 4 years and so fit plausible. Also consistent with clinical opinion.
PFS	Gompertz	Gompertz	Log-normal	Gompertz best statistical fit but not clinically plausible. Compared with KEYNOTE-177 is conservative selection.
Endometrial				
OS	Generalised gamma	Log-normal	Log-logistic	Generalised gamma provides too long a tail to be clinically plausible. Log-logistic has adequate statistical fit, good fit to the hazards and more conservative than log-normal.
PFS	Generalised gamma	Generalised gamma	Generalised gamma	Other curves provide implausible tails and gen-gam is best fit.
Gastric				
OS	Gompertz	Gompertz	Log-normal	Gompertz has more of a tail and cure fraction but log-normal good statistical fit and consistent with clinical opinion (conservative).
PFS	Generalised gamma	Generalised gamma	Log-normal	Gen-gam and Gompertz have better stats fits but they cross OS and would not be clinically plausible.
Small intestine				
OS	Gompertz	Gompertz	Log-logistic	Gompertz is not clinically plausible in terms of extrapolation (too long a tail). Log-logistic plausible and good fit.
PFS	Gompertz	Gompertz	Generalised gamma	Based on fit Gen-gam is reasonable and produces clinically plausible extrapolations (good fit to hazards etc).
Cholangiocarcinoma				
OS	Log-normal	Exponential	Log-normal	Gen-gamma has a very long tail and clinically less plausible. Log-

				normal good balance between fit and clinical plausibility.
PFS	Generalised gamma	Generalised gamma	Log-normal	Gen-gamma crosses OS too early and not plausible, log-normal more plausible and reasonable fits.

PFS piecewise BHM model information (f, g and h)

There is a strict rationale for the cut point chosen for the piecewise BHMs scenarios and that is explained above. Information related to patient numbers and events death/progression before and after the cut point are shown below.

The full breakdown in terms of fit stats and overlayed parametric fit plots are shown in appendix section J.2.1.2, as expected the fit to the tails after the 10-week cut point is significantly improved in all cases except the biliary site where the parametric fits tend to be higher than the end of the KM. Since the piecewise approach better captures the pembrolizumab PFS hazard function, this method predicts improved outcomes versus the standard BHM method used in the base case, the impact of which was explored in scenario analyses.

It is not clear what provide justification “per treatment” was requesting. Since comparator PFS outcomes in the base case are modelled using separately fitted parametric distributions, the choice of extrapolation approach for pembrolizumab does not impact comparator outcomes.

The primary justification for exploring a piecewise analysis of PFS was that the first protocol defined imaging timepoint occurred at 9 weeks from the date of allocation in both KN-164 and KN-158 which resulted in a sharp change in the hazard function not captured by standard parametric distributions. Using an earlier cut-point would not capture the feature described above. Using a later time point would likely produce more optimistic extrapolations of PFS outcomes since the PFS hazard is shown to steadily decline over time. The base case analysis therefore provides the most conservative approach. The piecewise analysis with a cut-point of 10 weeks is likely the most suitable method to appropriately capture the observed hazard function and results indicate a modest improvement in the ICER compared to the base case, as shown in the CS scenario analysis (Section B.3.11.3, Figure 46).

Table 33 Patient N and n of death or progression events before and after BHM piecewise cut point

	N at risk, start	N events from start to 10 weeks	N at risk, 10 weeks	N events after 10 weeks
CRC	[redacted]	[redacted]	[redacted]	[redacted]
Endometrial	[redacted]	[redacted]	[redacted]	[redacted]
Gastric	[redacted]	[redacted]	[redacted]	[redacted]
Small intestine	[redacted]	[redacted]	[redacted]	[redacted]
Cholangiocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]

B 7. Priority question: Given that pembrolizumab for patients with colorectal cancer was assessed in a separate trial (KEYNOTE-164) with a relatively large sample size compared to other tumour sites.

a) **Please justify why the treatment effectiveness of pembrolizumab in colorectal cancer was not modelled separately from other tumour sites in the company's base-case.**

b) **Please provide this analysis (joint distributions if indicated) as a scenario or base-case analysis in an updated economic model, supported by guidance from NICE TSD DSU 14 and 21.**

The scenario whereby the efficacy (OS, PFS) for each tumour site in KEYNOTE-158 and KEYNOTE-164 is treated independently is programmed into the model and presented in scenario analyses (independent parametric fits). This scenario paired with selecting results by tumour site and pairwise comparisons are equivalent to modelling a comparison (or tumour site) independently.

Fitting a BHM to a basket trial that also included the CRC cohort would be ideal, however a case can be made that the two trial designs and populations are very similar and so warrant an exploration of this sort of multilevel modelling approach. The inclusion/exclusion criteria differ between the two trials to the extent that they specify different pre-treatments (but the same line) relevant to the pathways but are otherwise very similar in terms of included/excluded patients (see Table 10 of the submission Document B). Pembrolizumab dosing and treatment schedules were also the same between trials and monitoring almost identical. It is important to note

that CRC as a total proportion of the cohort that the BHM model is applied to is not too dissimilar from the proportion in the population (see Table 43 of Document B).

Additionally, if you view the KMs for different tumour sites (see Figures 16 and 28 in Document B) CRC tends to be in the middle of the pack and so is less likely to skew results either way; indeed, the smaller sites tend to be on the edge of the pack of KM curves.

B 8. Priority question: Analyses of comparator survival outcomes were informed by published studies identified by the clinical SLR.

a) **Please justify the data sources used to inform comparator estimates per tumour sites and also discuss potential alternatives.**

b) **Please discuss limitations to the data sources per tumour site that are currently used to inform comparators estimates.**

c) **Please use comparative evidence (i.e. both pembrolizumab and relevant comparator) from KEYNOTE-061 for gastric tumours, provide survival analyses (joint distributions if indicated) supported by guidance from NICE TSD DSU 14 and 21 and provide this as a scenario or base-case analysis in an updated economic model.**

d) **If available, please also use comparative evidence for other indications as requested in question c and provide these as scenario or base-case analyses in an updated economic model.**

Please see the response to A44 which discusses alternative sources of comparator evidence. As discussed, the key downside is the lack of MSI-H/dMMR selected sources of evidence.

Analysis of KEYNOTE-061 shows the relative effects of pembrolizumab versus paclitaxel for both OS and PFS are greater than when a naïve comparison of KEYNOTE-158 pembrolizumab vs. KEYNOTE-061 is considered (see response to A32 above). To demonstrate the impact on the cost-effectiveness results a scenario has been included in the revised economic model which applies hazard ratios derived from KEYNOTE-061 to pembrolizumab outcomes generated by the BHM

approach. Given these results indicate the current approach is conservative versus the analyses requested here, further analyses have not been conducted.

The submitted economic model makes a representative use of the available data. Alternative combination of sources for comparator evidence could be used in a small number of cases where FOLFIRI/FOLFOX is a comparator, but as discussed in response to A44, this is unlikely to make much difference.

B 9. Priority question. It is unclear if the estimation and choice of (parametric) survival models are fully consistent with reported guidance from NICE DSU TSD 14 and 21 on (flexible methods for) survival analyses. For example, no external validation against long-term (real-world) data was provided for the selected OS and PFS curves in the intervention and comparator arms. Please provide, for OS, PFS and time to treatment discontinuation (TTD) for both aggregated and individual tumour sites and separately for the intervention and comparators:

a) **Tables with the numbers of patients at risk, per 3 months.**

b) **To examine the proportional hazard assumption:**
    i. **Plot the scaled Schoenfeld residuals versus time (all survival curves)**
    ii. **Plot the log cumulative hazard versus log time**

c) **To examine the heuristics of the hazard function over time:**
    i. **Plot the smoothed hazards over time**

d) **To examine diagnostics of parametric survival models (using the observed data):**
    i. **Plot the cumulative hazard versus time**
    ii. **Plot the log smoothed hazard versus time**
    iii. **Plot the standard normal quartiles versus log time**
    iv. **Plot the log survival odds versus log time**

e) **OS and PFS KM data of the comparator arms for the different indications is limited and the MSI-H/dMMR status for the majority of these patients is unknown. To examine the validity of the extrapolation beyond the KM data, please provide, for both pembrolizumab and the comparators, supporting evidence that the extrapolations are consistent with relevant external data and expert opinion. In case of expert opinion, please provide a full description of the methods and results of the expert consultation conducted.**

f) **Please justify the selection of the approaches to estimate and extrapolate OS, PFS, and TTD, taking into account the responses to the preceding questions as well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.**

g) **As suggested in NICE DSU TSD 14, please provide "substantial justification" in case different types of parametric models are used for different treatment arms.**

Response to a, b and c

The location of each of these are provided in the original submission documents and are listed out in the tables below, if unavailable in the submission they have been provided here.

Table 34 Location details for patients at risk (OS, PFS and TTD curves)

Treatment arm	Tumour site	Treatment	Endpoint	Document and location
Pembrolizumab	All tumour sites included within same figure	Pembrolizumab	OS	Document B, Figure 16, Section B.3.3.5.1
			PFS	Document B, Figure 28, Section B.3.3.6.1
			TTD	Document B, Figure 40, Section B.3.3.7.1
Comparator	Gastric	Paclitaxel	OS	Appendix P, Figure 7
			PFS	Appendix P, Figure 10

		FOLFIRI	OS	See below (Figure ***9***)
			PFS	See below (Figure 10)
	Small intestine	Nab-paclitaxel	OS	Appendix P, Figure 13
			PFS	Appendix P, Figure 16
	Cholangiocarcinoma	FOLFIRI	OS	Appendix P, Figure 19
			PFS	Appendix P, Figure 22
		FOLFOX	OS	See below (Figure 11)
			PFS	See below (Figure 12)
	Endometrial	TPC	OS	Appendix P, Figure 31
			PFS	Appendix P, Figure 34
	CRC	Pooled FOLFOX/ FOLFIRI	OS	See below (Figure 13)
			PFS	See below (Figure 14)
		TAS-102	OS	See below (Figure 15)
			PFS	See below (Figure 16)

Figure 9 Gastric FOLFIRI OS KM

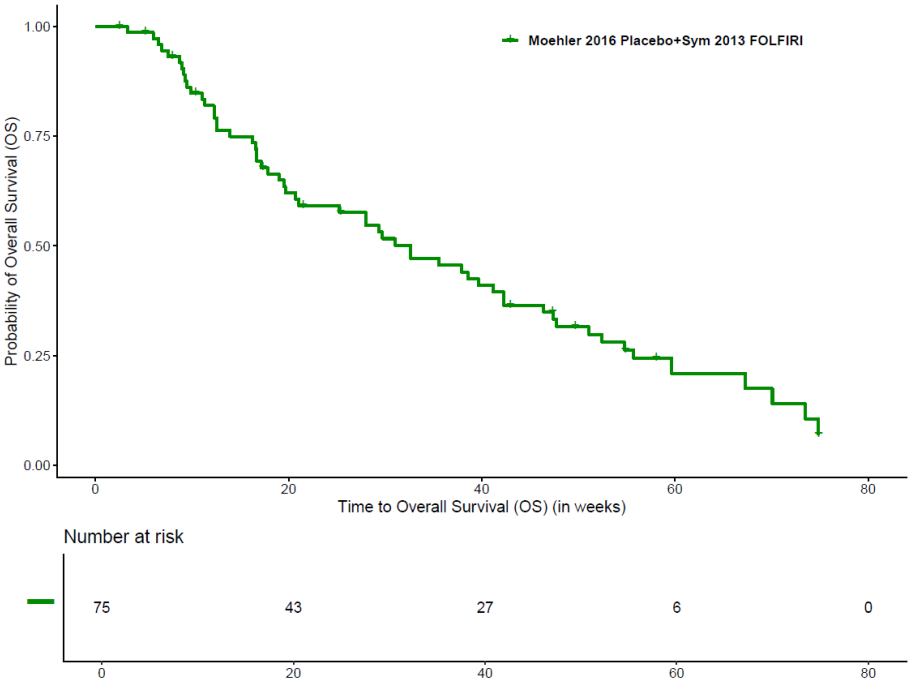


Figure 10 Gastric FOLFIRI PFS KM

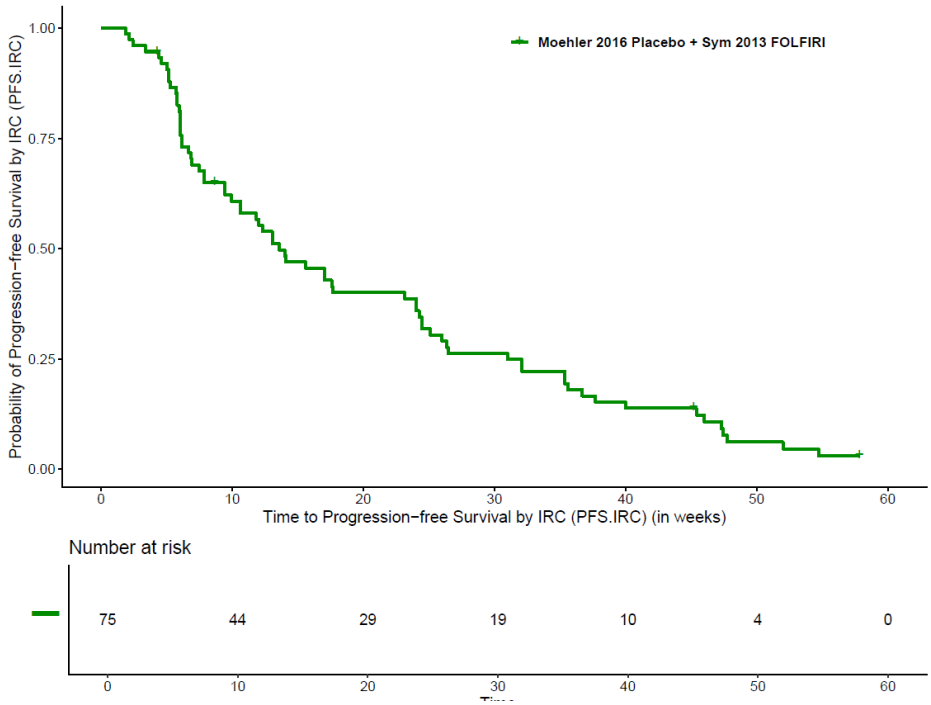


Figure 11: Cholangiocarcinoma mFOLFOX OS KM

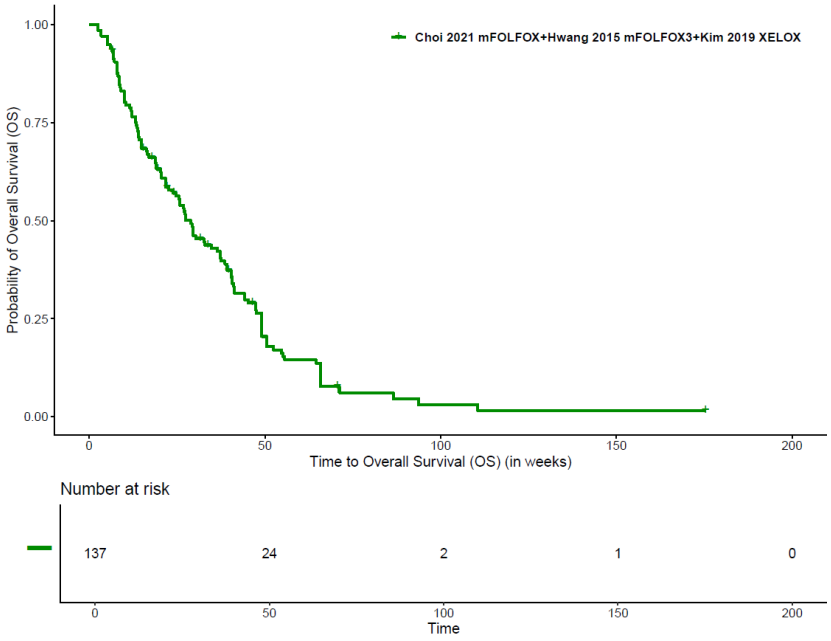


Figure 12: Cholangiocarcinoma mFOLFOX PFS KM

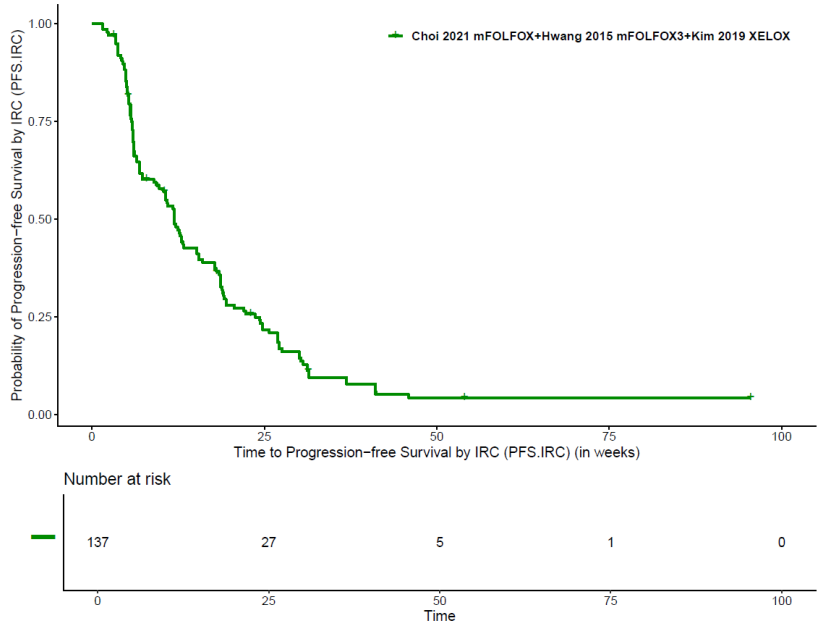


Figure 13: CRC pooled FOLFOX/FOLFIRI OS KM

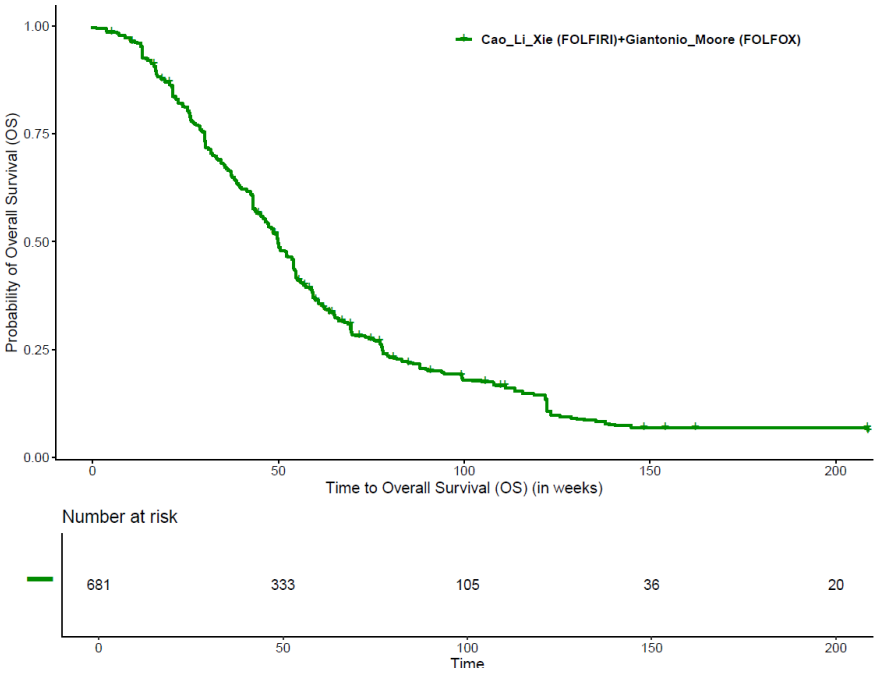


Figure 14: CRC pooled FOLFOX/FOLFIRI PFS KM

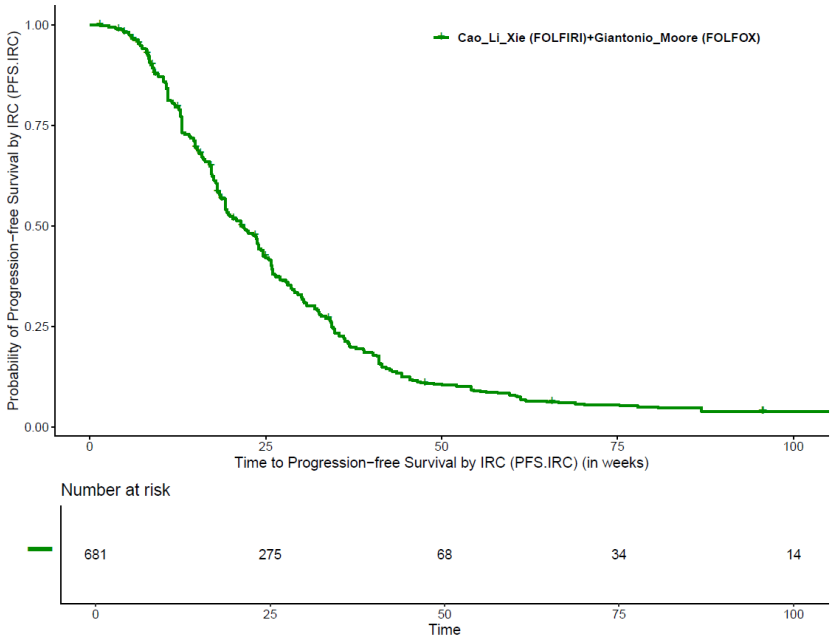


Figure 15: CRC TAS-102 OS KM

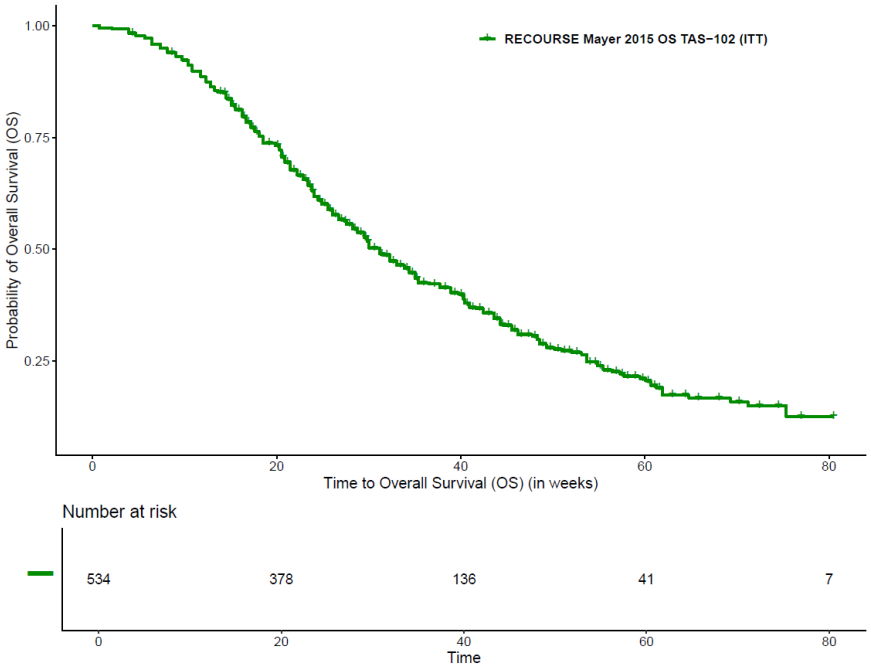


Figure 16: CRC TAS-102 PFS KM

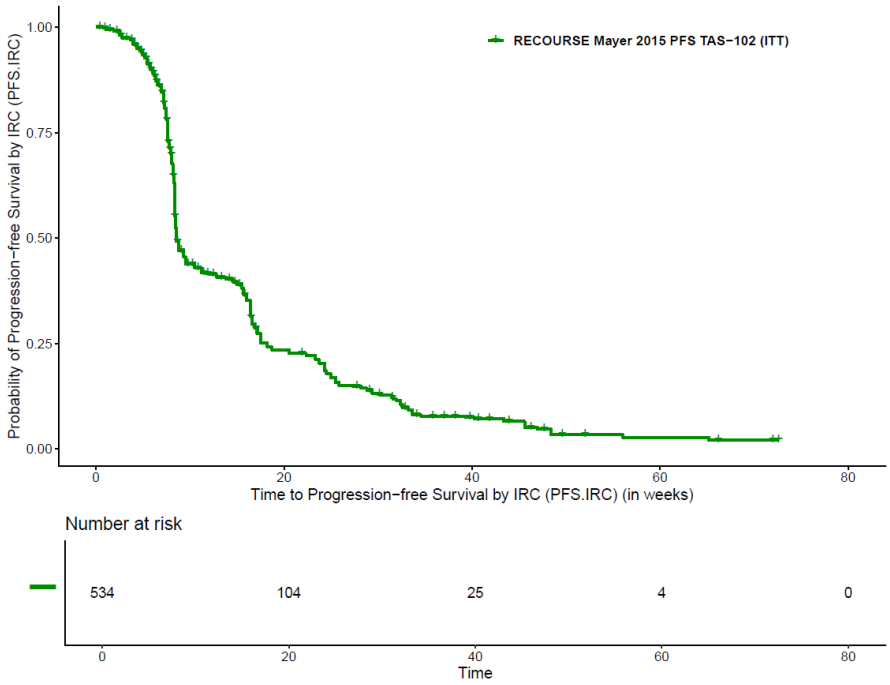
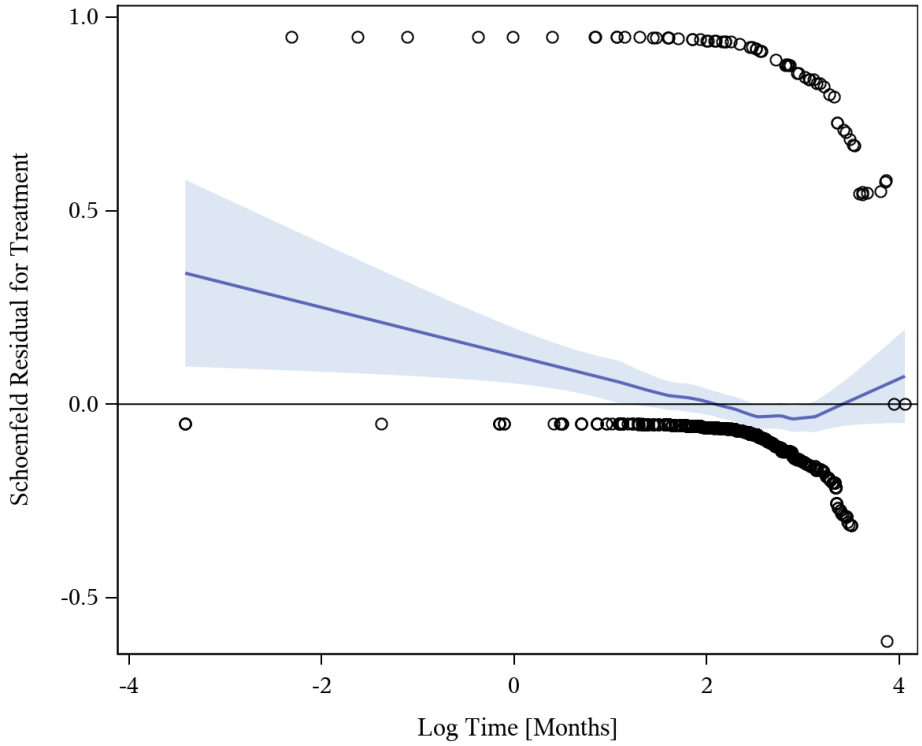


Table 35 Location details for proportional hazard plots (OS and PFS curves)

Tumour site	Treatment comparison (pembrolizumab vs)	Endpoint	Document (Appendix P) location	
			Schoenfeld residuals	Log cumulative hazard plots
Gastric	Paclitaxel	OS	Figure 9	Figure 8
		PFS	Figure 12	Figure 11
	FOLFIRI	OS	Figure 3	Figure 2
		PFS	Figure 6	Figure 5
Small intestine	Nab-paclitaxel	OS	Figure 15	Figure 14
		PFS	Figure 18	Figure 17
Cholangiocarcinoma	FOLFIRI	OS	Figure 21	Figure 20
		PFS	Figure 24	Figure 23
	FOLFOX	OS	Figure 27	Figure 26
		PFS	Figure 30	Figure 29
Endometrial	TPC	OS	Figure 33	Figure 32
		PFS	Figure 36	Figure 35
CRC	Pooled FOLFOX/ FOLFIRI	OS	See below (Figure 17)	Figure 38
		PFS	See below (Figure 18)	Figure 40
	TAS-102	OS	Figure 42	Figure 43
		PFS	Figure 46	Figure 45

Figure 17: OS Diagnostic Plot Schoenfeld Residuals for Treatment vs. Log Time for Overall Survival MSI-H Participants with Colorectal Carcinoma (All-Participants-as-Treated Population)



Study KN164, Database Cutoff Date: 19FEB2021
Selected comparators: FOLFIRI/FOLFOX/FOLFOX4/mFOLFOX-6 based on Xie et al. 2014, Moore et al. 2016, Li et al. 2018, Giantonio et al. 2007, Cao et al. 2015, Aparicio et al. 2022, mAPAT population
mAPAT: modified All-Participants-as-Treated
Solid line represents LOESS (Locally Estimated Scatterplot Smoothing) curve. Area around the solid line shows 95% CI

Figure 18: PFS Diagnostic Plot Schoenfeld Residuals for Treatment vs. Log Time for Overall Survival MSI-H Participants with Colorectal Carcinoma (All-Participants-as-Treated Population)

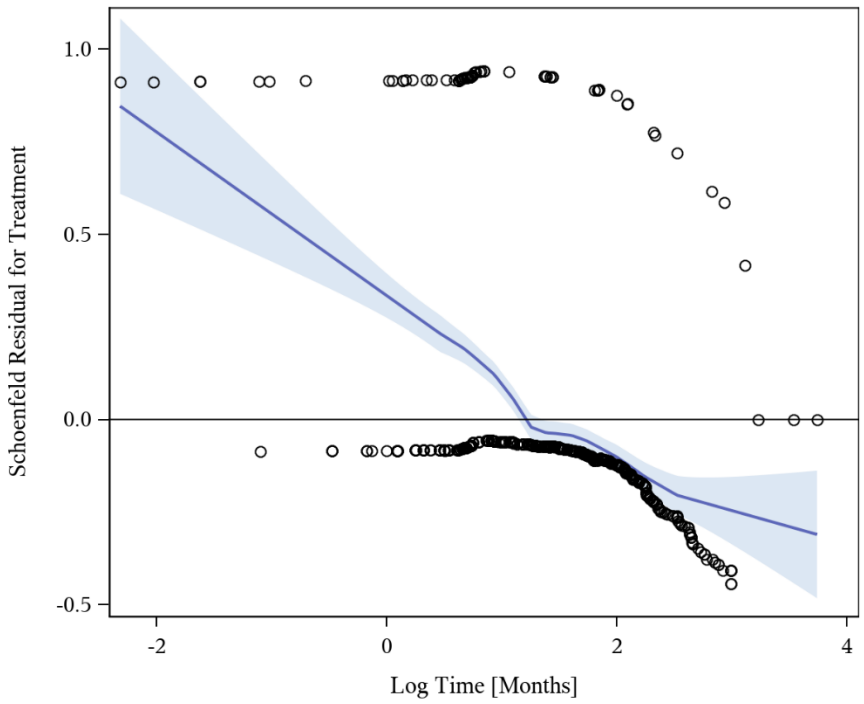


Table 36 Location details for smoothed hazard plots pembrolizumab (OS and PFS curves)

Tumour site	Endpoint	Document (Appendix J) location
Gastric	OS	Figure 15
	PFS	Figure 30
Small intestine	OS	Figure 17
	PFS	Figure 32
Cholangiocarcinoma	OS	Figure 19
	PFS	Figure 34
Endometrial	OS	Figure 13
	PFS	Figure 28
CRC	OS	Figure 11
	PFS	Figure 26

Response to d

MSD does not believe these plots, particularly given the programming time involved, will provide any additional utility over what has already been provided (i.e. the standard diagnostic plots that are usually considered): Schoenfeld Residuals plots, log cumulative hazard plots and raw hazard plots (against time).

Response to e

To account for uncertainty in the evidence base, various methods were used to validate the pembrolizumab and comparator extrapolations.

For the comparator arm, the observed OS and PFS data for each tumour site was relatively mature (from the Kaplan Meier OS curves, <15% remained alive in all tumour sites) and there were only small differences between the extrapolations. The consistency in the extrapolations translates to there being limited uncertainty around the survival estimates.

OS and PFS data collected for patients treated with pembrolizumab were also fairly mature; however, as a function of the profound improvement in survival outcomes achieved by treatment with pembrolizumab, a significant proportion of patients remain at risk at the end of the follow-up period. Compared to the comparator arm,

there was greater uncertainty associated with the resulting extrapolations, necessitating extensive validation efforts.

Clinical opinion was in the format of an advisory board. A description of this, including the number of experts attending and the topics discussed, was provided in Document B, Section B.3.14.1.1. Where expert opinion was given on the most plausible survival extrapolations for the comparator arm, this is noted in Section B.3.3.5.2 for OS and B.3.3.6.2 for PFS. For pembrolizumab, this is noted in Section B.3.3.5.1 for OS and B.3.3.6.1 for PFS. See response to B6 for an example of the type of validation slide that was presented.

In Document B, Section B.3.14.1.3 was dedicated to comparing the modelled survival data with those from previous relevant literature, given the confidentiality of survival data in previous NICE TAs. Finding relevant literature with published survival curves in patients with MSI-H/dMMR disease was limited and validation was only possible for the endometrial and gastric tumour sites.

Response to f

As described in Document B, Section B.3.3.4, in accordance with the NICE DSU TSD 14 guidance on survival analyses, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalized gamma) were explored for the extrapolation of OS and PFS KM data. Generalized gamma could not be explored for BHM because the model consistently failed to converge.

Per the Survival Model Selection Process Algorithm:

- Log-cumulative hazard plots were compared to examine the proportional hazard assumption (as noted in response to B9b)
- For each comparator, these showed violation of the proportional hazard assumption (i.e. the plots were not parallel)
    - Given 1) the proportional hazards assumption was violated in all cases, 2) the impact of population adjustment for observed confounders (via MAIC) was negligible and 3) flexible methods to derive time-varying

HRs were not feasible, comparator survival outcomes were modelled using independently-fitted parametric survival models

- A detailed explanation around the rationale for using BHM for pembrolizumab is provided in Section B.3.3.3.1.1

- The observed OS and PFS data for both pembrolizumab (and less so for comparator arms) were incomplete; therefore, the following steps outlined in the algorithm were considered:
  - **Visual inspection** – *visual inspection of the curves plotted against the observed KM data was done, as presented in Sections B.3.3.5.1 and B.3.3.5.2 for OS of pembrolizumab and comparator arms, respectively, and B.3.3.6.1 and B.3.3.6.2 for PFS of pembrolizumab and comparator arms, respectively*
  - **External data** – *validation against published long-term survival data, as discussed in response to B9e. In addition, the hazards of PFS and OS events were set to always equal or exceed the general population mortality hazard*
  - **Clinical validity** – *clinical plausibility for both short- and long-term estimates of survival, based on clinical expert validation, as discussed in response to B9e*
  - **AIC/BIC** – *considered to determine best statistical fit for comparator curves in Sections B.3.3.5.2 for OS and B.3.3.6.2 for PFS. The deviance information criterion (DIC) was used to determine goodness of fit for the BHMs used for pembrolizumab (Sections B.3.3.5.1 for OS and B.3.3.6.1 for PFS)*
  - **Log-cumulative hazard plots** – *these were compared to examine the proportional hazard assumption (as noted in response to B9b). Smoothed hazard plots of the observed pembrolizumab data are also provided to examine the heuristics of the hazard function over time, as noted in response to B9c*

- **Other suitable tests of internal and external validity** – *internal validity was further assessed by comparing extrapolated model outcomes with the observed KM data for pembrolizumab and comparators (Appendix J, Table 84). Furthermore, given the innovative nature of the BHMs used, these were thoroughly validated through double programming and visual inspection of the diagnostic, marginal posterior distributions, and model predictions*

- **Consider duration of treatment effect** – *treatment effect waning was conservatively applied in the base case and was set to start after 7 years (2 years past the end of the observed trial period) to acknowledge uncertainty in the assumption of a continued treatment effect, and to reflect the recommendations of EAGs in previous appraisals of pembrolizumab*

Published TTD KM data for comparator therapies were largely unavailable (either unreported in the published literature or redacted in previous NICE TAs). Therefore, parametric survival models used to extrapolate these data, based on TSD 14 guidance, was not possible (as discussed in Document B, Section B.3.3.7.2).

For pembrolizumab, TTD data for each tumour site were complete and therefore extrapolation was not required. Instead, the KM data were used directly in the model.

Response to g

Selecting individual curves for each arm that were clinically plausible with good visual and statistical fit was prioritised over ensuring consistency in the curve selections across treatment arms. This was considered acceptable due to the different mechanisms of action of pembrolizumab and comparator therapies, and given the clear observed differences in the OS and PFS data and clinical expectations around long-term survival projections.

In NICE DSU TSD14, it states that “if different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis”. This is the rationale used in our economic analysis. During the conducted advisory board, clinical experts validated the selected

curves for both pembrolizumab and the comparators and confirmed that the extrapolations were clinically plausible.

Although not specifically referring to the use of different parametric models for different treatment arms, the following quote from NICE DSU TSD21 acknowledges the different and more complex hazard functions associated with immunotherapies that are not typical of chemotherapies: “The advent of immuno-therapy treatments for oncology has resulted in an increase in the use of complex survival models, because delayed responses to treatment and the existence of long-term survivors have been hypothesised to result in complex hazard functions”.

As discussed in Section B.3.3.4, the distributions selected to extrapolate pembrolizumab survival outcomes were consistent with the clinical consensus that there is a ‘functionally cured’ proportion of patients across tumour sites that would be expected due to the immunomodulatory effects of pembrolizumab. The clinical feedback regarding functional cure was corroborated by assessment of the observed hazard function for pembrolizumab in each tumour site, showing the hazard steadily declining to a negligible value at the end of the follow-up period. Although no flexible approaches to explicitly model a cure assumption were implemented, the mechanism of action unique to immunotherapies was considered in curve selection and assessment of plausibility of extrapolations.

Notwithstanding the above justification, the model results were found to be insensitive to alternative comparator OS and PFS selections and showed a sustained benefit for pembrolizumab compared with chemotherapy for each tumour site. Again, this was consistent with clinical expectations.

B 10. Priority question. The company implemented waning of the pembrolizumab treatment effect between 7 and 9 years in its economic model.

a) **Please provide implied hazard ratio plots for PFS and OS versus time for both aggregated and individual tumour sites with numbers of patients at risk over time to justify this assumption.**

b) If indicated by the implied hazard ratio plots, please provide an updated economic model and scenario analyses exploring treatment waning to kick in at earlier time points.

Plots of the implied hazard ratio for overall survival and progression free survival are provided for pembrolizumab and tumour site-specific comparators in Figure 19 to Figure **28**.

The hazard ratio plots for overall survival indicate that the hazard ratio decreases (i.e. the hazard ratio increasingly favours pembrolizumab as it becomes further away from 1) quite rapidly initially, before subsequently stabilising (the time points at which the hazard ratios stabilise differ by tumour site) for a number of years up until year 7. The plots help to demonstrate the implausibility of the treatment effect waning assumption, illustrated by the drastic jump in hazard ratio at 7 years when the assumption kicks in. For tumour sites with multiple comparators, the hazard ratio at 9 years may not equal exactly 1. This is due to how this is programmed in the model as pembrolizumab hazards are waned to a single comparator.

Please note that it was not feasible to provide aggregate plots within the available time and MSD does not believe this will add any value to the exercise. Separately, plots of the predicted smoothed hazard function versus the empirical hazard are provided in response to question B9.

It is important to emphasize that there is little evidence to support treatment effect waning based on the observed data from KN-164 and KN-158. There appears to be no noticeable change in the shape of the empirical hazard function in response to treatment discontinuation for overall survival for any of the tumour sites (Appendix J, Question B9). However, given the lifetime time horizon and limited follow up of the trials, maintenance of the pembrolizumab treatment effect is uncertain and this uncertainty has been mitigated by the current base case analysis which adopts a highly conservative assumption that 100% of the pembrolizumab treatment effect being is removed by 9 years. We believe that the exploratory scenario analysis, in which treatment effect waning is excluded provides a more accurate reflection of the long-term outcomes for patients treated with pembrolizumab. Therefore, the

economic model has not been updated to include any alternative treatment waning assumptions.

Figure 19: CRC - OS - HRs

Figure 20: Endometrial - OS - HRs

Figure 21: Gastric - OS - HRs

Figure 22: Small Intestine - OS - HRs

Figure 23: Cholangiocarcinoma - OS - HRs

Figure 24: CRC - PFS - HRs

Figure 25: Endometrial - PFS - HRs

Figure 26: Gastric - PFS - HRs

Figure 27: Small Intestine - PFS - HRs

Figure 28: Cholangiocarcinoma - PFS - HRs

B 11. Pembrolizumab TTD is currently modelled directly using the KM-data from KEYNOTE-164 and KEYNOTE-158. Published TTD KM-data was unavailable for most comparators and therefore either an exponential distribution was fitted to the median time on treatment (ToT), or PFS was used as a proxy for TTD if the median ToT was not reported.

a) In line with OS and PFS, please model pembrolizumab TTD by fitting fully parametric survival models to the KM-data and justify your choice of curves.

b) For all comparators, please provide an updated economic model and scenario analyses assuming PFS as a proxy for the modelling of TTD.

Pembrolizumab TTD data are fully mature and therefore there is no need to fit parametric survival models to extrapolate outcomes.

A revised economic model has been provided where a scenario is explored using PFS as a proxy for all comparator TTD outcomes. Results for this scenario bias against the comparator as PFS as a proxy may overestimate TTD for some comparators where the available published data suggests some patients would discontinue therapy prior to progression.

B 12. According to the CS, the company used trial-based estimates to aggregate the individual tumour site results for pembrolizumab in its base case. In a scenario analysis, tumour site distributions were based on UK epidemiological data in combination with published sources, in which cancer incidences were identified for each tumour site and were adjusted to account for the proportion of patients remaining eligible for further active therapy.

a) Please further elaborate on the appropriateness of the selected sources of epidemiological data.

b) Please elaborate on how these data were adjusted to account for disease stage and treatment pathway progression.

Table 42 in Document B summarises the tumour site distribution used in the base-case (trial calculated) and those calculated from epidemiological data and these calculations epidemiological data by cancer/tumour type, line and progression on previous therapy and finally proportion that are MSI-H. The BIM document and BIM (sheet Epidemiology) will be provided with all the relevant calculations.

Adverse Events

B 13. The company did not include AE disutilities in their base-case analysis assuming that the disutility resulting from AEs would be captured in the EQ-5D data. As section B.3.4.1. details, patient-reported outcome (PRO) measurements decreased in frequency after the first four cycles (every three cycles until 9 months and every four cycles thereafter). Based on the 1-week duration of AEs that is

assumed in the economic model, AEs could occur and disappear within the time between PRO measurements. Based on this, please reflect on the plausibility of the assumption that all AEs would be captured in the EQ-5D data informing HRQoL in the economic model.

This collection schedule for PRO outcomes including EQ-5D is consistent with other oncology trials and also includes some collection post discontinuation, which is not always the case. Scenario analyses are explored that include comprehensive AE disutility's, the value and duration of which are based on previous literature and appraisals. This scenario analysis makes very little difference as is expected.

B 14. Medicines.org.uk (https://www.medicines.org.uk/emc/product/2498) lists numerous AEs of pembrolizumab as being very common (anaemia, hyperthyrodoidism, diarrhoea, nausea, vomiting, fatigue) defined by an incidence in more than 10/100 of treated patients. Table 62 of the CS suggests that none of the serious AEs have an incidence higher than 10%, while several of them are listed on the above website. KEYNOTE-042 for pembrolizumab (based on committee papers for TA760) also resulted in higher incidence rates for several AEs, while having a larger population size. Please justify the difference between AEs that are reported by public sources and by those reported in the CS.

These public sources list AEs based on both published trial data and adverse event reporting and cover the wide range of diseases/indications pembrolizumab has an approved license in to date and so are not necessarily relevant to this indication (or the related pivotal trials). In addition, Table 62 only includes Grade 3+ AEs, which will limit incidence.

B 15. Table 62 provides AE profiles per disease area. The EAG is unsure about the extent to which drug-related AE profiles commonly vary between diseases. Please explain the clinical reasoning behind differences in AE incidences across tumour sites

The overall number, type, and frequency of AEs and serious adverse events (SAE) reported are generally consistent with the well-known safety profile of pembrolizumab monotherapy and the underlying diagnosis of dMMR or MSI-H metastatic solid tumours. The relevant data is presented in section B.2.10 and related appendices.

B 16. Scenario analysis 12 in the CS applies AE disutilities in the economic model. The results of that analysis are depicted in Table 93 and show no difference in the incremental quality-adjusted life years (QALYs). Please explain why this analysis does not result in any difference in the incremental QALYs, and if applicable correct any mistake related to this and report any changes in the cost-effectiveness results.

Scenario 13 does make a difference to incremental QALYs, NHB and ICERs but only to a small extent – the change does not make a difference to results at 2dp (but can be better observed in the model scenario analysis sheet).

Quality of life

B 17. Priority Question: For tumour sites included in KEYNOTE-158, a time-to-death approach was used in the company's base-case to model HRQoL This approach seems inconsistent with the chosen model structure, which is based on disease status, and common modelling practices.

a) **Please justify the potential mismatch between the time-to-death approach to estimate HRQoL and the current disease status-based model structure as well as common modelling practices.**
    i. **Please provide any empirical evidence available to support this.**
    ii. **Reference 1 (advisory board minutes) is currently unavailable to the EAG. Please explain why clinical experts preferred the time-to-death approach.**

b) **Please provide any reference to the guidance used for the time-to-death approach.**

c) **Table 64 of the CS shows the number of observations per tumour site categorized by time-to-death. Please provide a similar table with observations per tumour site categorized by progression status.**

d) **Please provide a detailed description of how the time-to-death utilities were implemented in economic model.**

e) **Considering that the 360+ days utility from the time-to-death approach is substantially higher than the PF utility for colorectal cancer (CRC), please elaborate on the face validity of the time-to-death utility values.**

f) **Please provide an updated economic model and scenario analyses exploring modelling the quality of life (QoL) of patients by combining the 'health state' and 'time to death' approaches, e.g. by implementing end-of-life utility penalties**.

Rationale for TTD

The observed utility data is presented in Document B (Table 64) and shows that mean utility varies when patients are categorised into TTD categories and so there is a clear relationship between time-to-death and QoL. There is evidence that suggests that health state utilities can produce a poor fit to observed trial QoL if patient QoL varies significantly with closeness to death (see van den Hout WB, et al. JNCI 2006;98 (24):1786-94 and Hatswell AJ, et al. Health and Quality of Life Outcomes 2014;12:140).

At the ad-board after an introduction to how utility analyses are undertaken for modelling, visual representations of both the TTD and health state approaches were presented:

Among clinicians, both approaches were considered plausible but there was preference for the TTD approach because the utility trends associated with the time-

to-death approach are deemed more reflective of patient HRQL outcomes for pembrolizumab, which is associated with long survival tails and a functionally cured proportion. This was also supported by the health economics professor who suggested that a TTD approach may conceptually be better suited to capturing the longer post progression survival associated with Immunotherapies.

Breakdown of observations by progression status (FAS population)

As requested, number of observations broken down by progression status are shown below.

Table 37 Number of EQ-5D observations by progression status

Tumour site	Number of observations (total not missing EQ-5D score)	Number of observations PFS (including baseline)	Number of observations (PPS)	Number of observations (unknown progression status)
Endometrial	[redacted]	[redacted]	[redacted]	[redacted]
Gastric	[redacted]	[redacted]	[redacted]	[redacted]
Small intestine	[redacted]	[redacted]	[redacted]	[redacted]
Biliary (Cholangiocarcinoma)	[redacted]	[redacted]	[redacted]	[redacted]

TTD implementation in model

To apply time-to-death utilities in the economic model the proportion of patients within each cycle transitioning to the death health state is first calculated (Engine (1) Column AQ). Then for each of the TTD categories, the proportion of patients experiencing a death event in the next X cycles is calculated and multiplied by the total LYs accrued within the cycle (i.e. the proportion of patients still alive). These calculations are done in Engine (1) Column AY:BC. Since the treatment status relative to the time to death cannot be known and TRAEs should only be applied while patients remain on treatment, AE disutilities are not applied when the TTD utility option is selected.

CRC utility source compared with TTD

It must be remembered that the CRC source is from an external source (Grothey et al. 2013) and not the same dataset as the KEYNOTE-158 utility analyses. The Grothey et al. 2013 publication while used extensively in previous NICE appraisals in CRC only reports mean utility at baseline and at the end of treatment.

However, in general there is no inconsistency between the earlier category TTD utility being higher than the PFS utility for a given tumour site (or overall) and this is not uncommon. This may also support the rationale for the TTD approach in the context of immunotherapies, in that quality of life depends more on time from death than progression status (I.e. the correlation between death and progression is broken); there may be instances where a progressed patient who ends up living longer will have better quality of life than a patient who has yet to progress but who does not live as long.

However, importantly one of the key differences is that utility values from Grothey et al. 2013 were for patients treated with either regorafenib or placebo, compared to pembrolizumab in KEYNOTE-158. The difference between the two studies may reflect the improved health related quality of life experienced by patients treated with pembrolizumab versus other therapies. However, with the available data it is not clear what exactly is the cause of the observed difference.

It is not very clear what is meant by combining the “health state” and “time to death” approaches. Given the small sample sizes for some TTD categories, by tumour site, it was not possible to do a TTD regression analysis for each tumour site separately and so it would not be feasible to do a regression analysis that estimates utilities in categories related to both death and progression status by tumour site.

B 18. Priority Question: According to Section B.3.4.1 of the CS, patients completed a maximum of two observations post treatment discontinuation. As patients discontinued at the latest at disease progression, the utility measurements from the KEYNOTE-158 trial omit a significant part of the treatment population.

a) **Please reflect on the appropriateness of using these data to calculate utility across the population and indicate the potential bias caused by this.**

b) Please discuss why this approach is preferrable to other approaches including data from other trials.

The limited post-progression HRQL observations observed in KEYNOTE-158 is a common limitation of oncology clinical trials; there is always a trade-off between using a source for utilities consistent with the OS/PFS source versus an external source that may or not be more robust. Furthermore, the model adjusts extrapolated health state utilities to account for age-related decline in HRQL and therefore some of the decline in HRQL which may not be captured within the KEYNOTE-158 data may already be accounted for.

In cases where the available data provides limited post-progression HRQL observations, a time-to-death approach provides a suitable alternative as included within the company base case. KEYNOTE-158 provided the most robust available data to inform patient HRQL for patients with previously treated MSI-H/dMMR solid tumours treated with pembrolizumab. In the absence of robust published data for this population of patients, the approach to apply pembrolizumab health state utilities to comparators is likely to overestimate comparator HRQL and provide a highly conservative cost-effectiveness estimate. In addition, this approach would also underestimate the true severity of disease informing the NICE decision modifiers.

B 19. Appendix G of the CS details that multiple studies were identified to inform utility values for patients with CRC. The company selected Grothey et al. 2019 to inform CRC utility values.

a) Please justify why the study of Grothey et al. 2019 was preferred to other sources of utility values.

b) Please conduct scenario analyses with the other sources of utility values found in Appendix G and elaborate on how these compare to the base-case values currently used in the economic model.

The 15 other publications reporting utilities in CRC are shown in Table 8 in appendix G and these are fully summarised in the subsequent sections (and Summary Table 9).

From Table 9, relevant health state utilities that both use EQ-5D as a method of elicitation and provide utilities for relevant health states (and for example are not means for irrelevant states) are summarised in the table below.

In the base-case given the lack of data from the KEYNOTE-164 trial to inform the CRC tumour site-specific utility values, the values of 0.73, 0.74, and 0.59 reported in Grothey et al. (2013) were used in the base case to inform HRQL for the PFS on treatment, PFS off treatment, and the PD (on and off treatment) states, respectively. This was chosen to be reasonably conservative.

It is clear from the summary of potentially relevant CRC utilities below that the base-case selections are conservative. All reported PFS utilities from alternative studies show values higher than 0.73 except the Nivo+ipi off treatment utility (TA716); however the latter is higher than the general post progression utility quoted. All PPS utilities are higher than 0.59 (apart from the AEG source for TA716 which is the same). Given the post progression and pre-progression survival advantage for pembrolizumab over the comparators in CRC, these alternative higher values will tend to improve cost-effectiveness.

Table 38 Summary of potentially relevant CRC PFS and PPS utility values

• **Study name** • **Country**	**Utility values**

• NICE_TA716 [NIVO+IPI] 2021
• UK
	• Health-related quality of life values applied in the economic model (Company's submission),
	  • On treatment NIVO+IPI mean utility: Undisclosed
	  • Off treatment, NIVO+IP mean utility: 0.69
	  • Pre-progression mean (SE) utility: 0.75 (0.08)
	  • Post-progression utility: 0.69 (0.07)
	• Values used by ERG in its base case:
	  • Post-progression mean utility values from CORRECT: 0.59
	• Utility values by health state observed in Checkmate 142, mean, (95% confidence interval)
	  • PFS: 0.839 (0.821,0.857)
	  • PFS, on treatment: 0.837 (0.818,0.856)
	  • PD: 0.850 (0.804,0.896)
	  • PD, on treatment: 0.728 (0.603,0.852
	  • PFS, off treatment: 0.872 (0.814,0.930)

• CADTH [Encorafenib] 2021
• Canada
	• Progression free state:
	  • Encorafenib + Cetuximab: 0.81
	  • Cetuximab + FOLFIRI/Irinotecan, FOLFOX and FOLFIRI: 0.79
	• Post progression state:
	  • Encorafenib + Cetuximab: 0.76
	  • Cetuximab + FOLFIRI/Irinotecan, FOLFOX and FOLFIRI: 0.76

• NICE_TA668 [Encorafenib+cetuximab] 2021 • UK	• Utility values (BEACON CRC August 2019 dataset) Mean (SD); SE Encorafenib with cetuximab, • Pre-progression (n= 1,344): 0.743 (0.195); 0.005319 95% CI: 0.732, 0.753 • Post-progression (n= 147): 0.622 (0.252); 0.020785 95% CI: 0.582, 0.663 BEACON CRC control arm FOLFIRI • Pre-progression (n= 591): 0.741 (0.193); 0.007939 95% CI: 0.725, 0.756 • Post-progression (n= 161): 0.631 (0.279); 0.021988 95% CI: 0.558, 0.661 Trifluridine-tipiracil; pre-progression: 0.742 Trifluridine-tipiracil; post-progression: 0.627

• Graham 2016
• US
	• Utility weights:
	  • Progression free, Pooled: 0.803
	• By treatment
	  • Panitumumab: 0.7962
	  • Cetuximab: 0.8096
	• Progressive disease
	  • Subsequent antitumor: 0.749
	  • BSC: 0.602

• NICE_TA307 [Aflibercept + irinotecan and fluorouracil-based therapy] 2014 • UK	• Progressed disease: 0.708

• Stein 2014
• Netherlands and UK
	• Utility index, mean (SD)
	  • Pre-progression: 0.741 (0.230)
	  • Post-progression: 0.731 (0.292)

Costs and resource use

B 20. Section B.2.3.1 states that pembrolizumab can be given for up to 35 cycles or until disease progression. However, the 'engine' sheet of the health economic model shows that some acquisition costs are calculated beyond 35 cycles and column CD indicates that some patients receive treatment after progression. Please justify the plausibility of these observations by the EAG in light of the assumptions above and if applicable correct any mistake related to this and report any changes in the cost-effectiveness results.

The base case analysis in the CS applies the TTD data as observed in the KEYNOTE-164 and KEYNOTE-158 trials by directly applying the KM function to the economic model. In a small number of case where the extrapolated PFS curve crosses the TTD KM this results in patients transitioning to the progressed-disease on treatment state where no stopping rule at 35 cycles is applied. Given that the trials did not allow treatment beyond progression this indicates that the extrapolated PFS curve for pembrolizumab may be underestimated.

A revised economic model has been provided with functionality to cap the TTD by the modelled PFS curve (see the bottom of the model controls sheet for new controls). This amendment therefore caps TTD by both PFS and OS, rather than just by OS as in the base case analysis. This improves the ICERs for pembrolizumab.

B 21. Section B.3.5.1.1.2 of the CS states that 'Consensus opinion on market shares was elicited from clinical experts'. This indicates that inputs were elicited from a group instead of interactions within individual experts. Reference 1 (advisory board minutes) is currently unavailable to the EAG.

a) Please describe the methodology used for expert elicitation according to Bojke's reference protocol for expert elicitation in HTA (https://pubmed.ncbi.nlm.nih.gov/34105510/).

b) Bojke's reference protocol for expert elicitation in HTA states that beliefs should be elicited from experts individually even if group interaction follows. Please confirm that inputs were elicited from a group instead of individuals and reflect

on impact this may have on the results of the elicitation procedure and the results of the model.

Tumour site distribution among the total population covered in the license was calculated from epidemiological data – clinicians were uncertain about estimating this at the ad-board and supported the epidemiological approach that was used in a scenario analysis. However, in contrast there seemed to be reasonable consensus about “market shares” for comparators within tumour sites and so the estimates derived via group clinical consensus opinion at the ad-board were used to inform this weighting in the model. It is true that these are uncertain, but that is why results have been presented transparently in several ways across document B and relevant appendices: weighted by overall indication, within tumour site and shown by comparator piecewise. Results are also easily accessible from the Results tables sheet of the model.

Results

B 22. Considering the CS base-case results.

a) For both the aggregated analyses and per indication, please provide a comparison of the observed survival as well as progression free survival (e.g. using restricted mean survival time; RMST) and the undiscounted life years (LYs) as well as undiscounted progression free LYs (estimated in the model) by filling out the Table below using different periods/truncation points (with justification) to calculate the RMST.

b.	c. **Observed**	d. **Modelled**	
e.	f. **Restricted mean survival time (RMST)**	g. **Estimated (lifetime time horizon)**	h. **Proportion beyond observed data**
i. **OS - RMST period / truncation point: XX months (selected based on XX)**			
j. XXX	k.	l.	m.
n. **Comparator**	o.	p.	q.
r. **Increment**	s.	t.	u.
v. **OS - RMST period / truncation point: XX months (selected based on XX)**			
w. XXX	x.	y.	z.
aa. **Comparator**	bb.	cc.	dd.
ee. **Increment**	ff.	gg.	hh.
ii. **OS - RMST period / truncation point: XX months (selected based on XX)**			
jj. XXX	kk.	ll.	mm.
nn. **Comparator**	oo.	pp.	qq.
rr. **Increment**	ss.	tt.	uu.
vv. **PFS - RMST period / truncation point: XX months (selected based on XX)**			
ww. XXX	xx.	yy.	zz.
aaa. **Comparator**	bbb.	ccc.	ddd.
eee. **Increment**	fff.	ggg.	hhh.
iii. **PFS - RMST period / truncation point: XX months (selected based on XX)**			
jjj. XXX	kkk.	lll.	mmm.
nnn. **Comparator**	ooo.	ppp.	qqq.
rrr. **Increment**	sss.	ttt.	uuu.
vvv. **PFS - RMST period / truncation point: XX months (selected based on XX)**			
www. XXX	xxx.	yyy.	zzz.
aaaa. **Comparator**	bbbb.	cccc.	dddd.
eeee. **Increment**	ffff.	gggg.	hhhh.

b) Please elaborate on the plausibility of the differences between observed and modelled outcomes (proportion accumulated beyond observed data) for:

   i. Pembrolizumab

   ii. the comparators

   iii. the increment

c) Regarding the model estimated differences between the intervention and the comparators (in terms of PFS, LYs and quality-adjusted life years

(QALYs)); please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence (NICE DSU TSD 19 recommendation 13).

Response to a and b

While it's not immediately clear what is being requested in the table, a summary has been provided comparing RMST of the observed KM function for KEYNOTE-164 and KEYNOTE-158 trials with the RMST of the modelled base case survival curve over the modelled time horizon (40 years), for both pembrolizumab and comparators within each tumour site. These are provided separately for overall survival outcomes (Table 39 to Table 43) and progression free survival outcomes (Table 44 and Table 48).

It was not feasible within the economic model to aggregate survival data for SoC or for the entire indication as this is done separately within the model. Modelled outcomes were not truncated and reflect the lifetime time horizon. Observed outcomes were effectively truncated at the maximum follow up period of the available trial data. Note that a new functionality has been added in the model so that these RMST outcomes are automatically generated when a new set of deterministic results are run (scroll right along the top of the OS and PFS sheets).

Table 39 Observed versus predicted survival outcomes - CRC OS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	
OS - RMST period / truncation point: 64 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
TAS-102	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Pooled FOLFOX/FOLFIRI	[redacted]	[redacted]	[redacted]

Increment	[redacted]	[redacted]	[redacted]

Table 40 Observed versus predicted survival outcomes - endometrial OS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	**Estimated (lifetime time horizon)**	
OS - RMST period / truncation point: 64 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Table 41 Observed versus predicted survival outcomes - gastric OS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	**Estimated (lifetime time horizon)**	
OS - RMST period / truncation point: 67 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Table 42 Observed versus predicted survival outcomes – small intestine OS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	
OS - RMST period / truncation point: 68 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Nab-paclitaxel	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Table 43 Observed versus predicted survival outcomes - cholangiocarcinoma OS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	
OS - RMST period / truncation point: 61 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
mFOLFOX	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
mFOLFIRI	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Table 44 Observed versus predicted survival outcomes - CRC PFS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	
PFS - RMST period / truncation point: 61 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
TAS-102	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Pooled FOLFOX/FOLFIRI	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Table 45 Observed versus predicted survival outcomes - endometrial PFS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	
PFS - RMST period / truncation point: 63 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Table 46 Observed versus predicted survival outcomes - gastric PFS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	
PFS - RMST period / truncation point: 65 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
FOLFIRI	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Table 47 Observed versus predicted survival outcomes – small intestine PFS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	
PFS - RMST period / truncation point: 59 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
Nab-paclitaxel	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

Table 48 Observed versus predicted survival outcomes - cholangiocarcinoma PFS

	Observed	Modelled	Proportion beyond observed data
	Restricted mean survival time (RMST)	Estimated (lifetime time horizon)	
PFS - RMST period / truncation point: 48 months (selected based on Pembrolizumab max follow-up)			
Pembrolizumab	[redacted]	[redacted]	[redacted]
mFOLFOX	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
mFOLFIRI	[redacted]	[redacted]	[redacted]
Increment	[redacted]	[redacted]	[redacted]

The tables provided indicate that a substantial proportion of the predicted pembrolizumab survival is accumulated after the observed follow up period. This is to be expected given that a large proportion of patients remained alive at the end of the follow up period, which is consistent with the clinical consensus that there is a proportion of patients across tumour sites that would be expected to achieve long-term durable survival. The proportion beyond the observed data varies between tumour site as a function of the observed data as well as the level of treatment effect waning applied based on the comparator predicted hazard function.

For progression-free survival, the same is true although the proportion accumulated beyond the observed period is less than overall survival due to the relative maturity of the data. Treatment effect waning moderates progression-free survival outcomes as they are programmed in the model to be capped by the overall survival curve.

For the comparators, the proportion of survival accumulated beyond the observed period is less than pembrolizumab. This is due to the poor prognosis for previously treated MSI-H/dMMR solid tumours patients treated with currently available therapies. For some comparators such as nab-paclitaxel in small intestine and mFOLFOX in cholangiocarcinoma, given that the overall survival data are almost completely mature, the proportion beyond the observed period indicates how well the

predictive distributions fit the observed data. This is even more the case for PFS. For some comparators this results in a negative percentage although the relatively small difference indicates the models fit the observed data relatively well.

The plausibility of the increment accrued after the follow up period is challenging to interpret due to the different follow up periods of the relevant clinical trials. Importantly, the increment should be interpreted as the proportion of survival outcomes accrued beyond the follow up period of the pembrolizumab trial. Therefore, the plausibility of these results is directly linked to the plausibility of the extrapolated pembrolizumab outcomes. Ultimately, the results reported in response to this question reflect extrapolated survival outcomes, which best reflect the available clinical data and, in the case of pembrolizumab, may underestimate the accumulated incremental survival benefit due to the exaggerated impact of treatment effect waning applied in the base case. However, it is also true that for tumour sites with smaller patient numbers such as cholangiocarcinoma and small intestine, the BHM is shown to potentially overpredict survival outcomes and therefore these two factors may act to counteract each other. Despite this, the benefits of the BHM methodology used to inform these survival outcomes far outweigh the perceived poor fit of the models to what are uncertain data from a small number of patients.

Response to c

The model estimates substantial differences between pembrolizumab and the tumour site specific comparators in both QALYs and LYs due to the profound improvement in both progression-free survival and overall survival outcomes. The quantitative estimates of the incremental QALY and LY gains for pembrolizumab are a function of the efficacy of the existing treatments as well as the observed outcomes for pembrolizumab in KEYNOTE-158 and KEYNOTE-164.

B 23. Please provide fully incremental analyses of all relevant comparators for the indications/tumour sites that include more than one comparator.

Fully incremental analyses by tumour site can be produced by the model (Results table sheet) and this is automatically plotted on a cost-effectiveness frontier. However, given this is not a multiple technology appraisal and the focus is on the

relative cost-effectiveness of pembrolizumab vs standard of care, it does not seem appropriate to provide fully incremental results.

B 24. Table 100 in Appendix J of the CS provides a summary of input parameters and how these were varied in the deterministic and probabilistic sensitivity analyses. Parameters informing treatment effectiveness are not included in this Table. Please explain whether and how parameters related to treatment effectiveness were included/varied in deterministic and probabilistic sensitivity analyses, and if not, please provide updated analyses including these parameters.

Parameters informing treatment effectiveness were informed either by standard parametric survival models or parametric survival models fitted in a Bayesian hierarchical modelling (BHM) framework. For standard parametric survival models, parameters were varied probabilistically by sampling from a multivariate normal distribution using the corresponding variance covariance matrix. For BHMs parameters were varied probabilistically by random sampling from the posterior distribution. Both methods allow uncertainty in the survival analysis to be captured within the economic model while preserving the correlation structure of the multivariate distributions. Treatment effectiveness parameters for both these types of models were not varied in OWSA as it is inappropriate to vary multivariate distributions in this way.

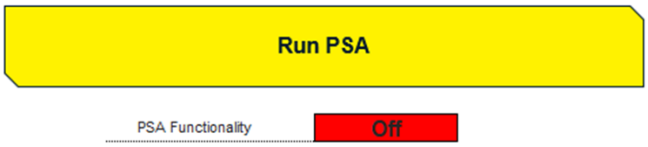
A full summary of included parameters can be found in the economic model. Pragmatically these were not included in Appendix J as the model includes nearly 1000 standard parametric survival model parameters and almost 260 BHM parameters.

B 25. To run the probabilistic sensitivity analyses in the economic model, several steps are required (e.g. loading in a file including PSA samples) and its run time is relatively long.

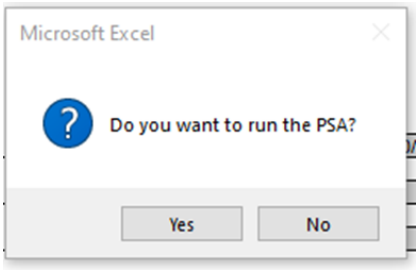
a) Please provide step by-step details of how to correctly implement the probabilistic sensitivity analyses in the economic model.

b) Please clarify whether there are straightforward adjustments that the EAG can incorporate to speed up the probabilistic analyses.

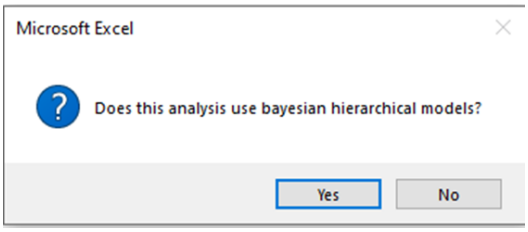
1) Click Run PSA button (having the PSA results functionality “Off” may reduce run time).



2) Click “Yes”



3) Click “Yes”



4) Download the “PSA BHM Samples” provided and select the “PSA BHM Samples” file from the file explorer. This action loads the posterior distribution samples which are then randomly sampled in the PSA.

5) The PSA should now begin to run.

6) Once the PSA has been completed, “Turn on PSA results” to view the analysis. Please note to view results for different tumour sites or different comparators the PSA does not need to be re-run.

No, the analysis took approximately 2 hours on an optimised PC which is deemed acceptable given the complexity and scale of the analyses and the decision problem. Code developed to run the PSA has been heavily optimised to ensure the runtime remains manageable. Ensuring PSA, OWSA and scenario analysis results functionality are switched off may reduce run time.

B 26. Table 93 of the CS reports the results of the scenario analyses for the overall indication pembrolizumab versus SoC. Please also provide the results of these scenario analyses separately per individual indication.

Appendix sections J4-J6 provides all cost-effectiveness results by individual comparison and tumour site. These are also easily obtainable by tumour site pairwise comparison in the Scenario Analysis sheet of the model by selecting tumour sites (instead of weighted average) and a comparator.

Severity

B 27. Please provide all cost-effectiveness results (per tumour site and aggregate) also without applying the QALY multiplier.

These results can be obtained by setting "Apply QALY weighting directly to the QALYs" to No in Model Controls and running deterministic analyses. This is for the originally submitted base-case model.

Table 49 Base-case results without QALY multipliers

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB
SoC	£33,758.60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,190	1.03

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.

Table 50 Histology specific results without QALY multipliers

Tumour site	Total costs (£)		Total QALYs		Incremental outcomes			
	Pembrolizumab	SoC	Pembrolizumab	SoC	Δ Costs (£)	Δ QALYs	ICER (£)	NHB
CRC	[redacted]	£44,237.61	[redacted]	[redacted]	[redacted]	[redacted]	£10,505	1.47
Endometrial	[redacted]	£24,352.13	[redacted]	[redacted]	[redacted]	[redacted]	£18,016	1.19
Gastric	[redacted]	£28,106.03	[redacted]	[redacted]	[redacted]	[redacted]	£26,682	0.19
Small intestine	[redacted]	£34,793.15	[redacted]	[redacted]	[redacted]	[redacted]	£25,592	0.43

Cholangiocarcinoma	[redacted]	£22,017.09	[redacted]	[redacted]	[redacted]	[redacted]	£20,995	0.61

Abbreviations: CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; SoC, standard of care.

B 28. The severity estimates depend on the company's own estimation of QALY gains in the different tumour sites (which are dependent on assumptions around utility estimations and survival analyses) and rely on evidence of patients with solid tumours but not with MSI-H/dMMR.

a) Please provide the severity estimates, i.e. Table 86 of the CS, but instead of using the time-to-death approach to utilities use the health state specific approach to utilities.

b) Please provide the severity estimates, i.e. Table 86 of the CS, but instead of using the BHM approach use the standard survival analysis approach.

c) Please discuss any evidence on survival or HRQoL of patients with MSI-H/dMMR under standard of care treatment and use this evidence for alternative severity calculations.

d) The company stated that *"QALY shortfall estimates provided in Table 86 are likely to drastically underestimate the true severity of the condition given that utility values used in the current analysis are expected to overestimate the quality of life of patients treated with existing treatments."* However, for CRC the expected QALYs are higher than those reported in previous TAs shown in Table 85 which seemingly contradicts this. Please elaborate on your reasoning.

HS approach instead of TTD and modifiers

The table below provides severity estimates using the health state by tumour site utility approach. Most notable differences are observed in the small intestine and cholangiocarcinoma tumour sites where higher health state utilities are observed. Given that shortfall estimates are on the boundary of the higher modifier cut-off there may be biases that have a significant impact:

- These are based on small numbers of observations and are therefore uncertain.
- They are also based on the pembrolizumab trial sources and so may be overestimated by reflecting patients in PFS on pembrolizumab and patients who have eventually been functionally cured by pembrolizumab.
- Most sources of comparator efficacy are not from MSI-H/dMMR selected sources and so may overestimate survival and so accrued QALYs.

Table 51 Summary of QALY shortfall analysis using health state by tumour site utility approach

Tumour site	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
CRC	13.58	[redacted]	[redacted]	[redacted]	1.2
Endometrial	11.32	[redacted]	[redacted]	[redacted]	1.2
Gastric	10.40	[redacted]	[redacted]	[redacted]	1.2
Small intestine	12.96	[redacted]	[redacted]	[redacted]	1.2
Cholangiocarcinoma	12.35	[redacted]	[redacted]	[redacted]	1.7
Abbreviations: CRC, colorectal cancer; QALY, quality-adjusted life year.					

In response to b, the BHM analysis estimates pembrolizumab survival outcomes. Changes in the approach to model pembrolizumab outcomes would not impact severity estimates.

Alternative severity calculations based on MSI-H/dMMR sources

In response to c, there have been two previous NICE appraisals in the MSI-H/dMMR population. One in endometrial cancer (TA779 dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency) and one in colorectal cancer (TA716 nivolumab with

ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency). Expected QALYs in the Current Clinical Management arm of TA779 were redacted and therefore have not been used to provide alternative severity estimates.

Baseline patient characteristics used in the cost-effectiveness analysis in TA716 were:

- Proportion male – 58.8%
- Age – 56.6 years

Therefore, the expected total QALYs for the general population according to the Schneider tool are 13.69 QALYs. Table 7 presents QALY shortfall estimates using the Schneider (2021) tool and survival and quality of life evidence from TA716.

Table 52 TA716 ERG base case severity estimates

Treatment arm	FOLFOX	FOLFIRI
Total QALYs	0.877	0.822
Proportional shortfall	93.58%	94.00%
QALY weight	1.2	1.2

CRC expected QALYs and other CRC sources

Since CRC is the only tumour site where published HRQL sources were used to inform the economic model we would expect that results are comparable between this and relevant submissions reported in Table 85. This is shown to be the case where total QALYs for FOLFOX and FOLFIRI in TA716 were 0.877 and 0.822, respectively. Results from submitted Document B (unweighted for decision modifiers) for the pooled comparator of FOLFOX/FOLFIRI were 0.84 total QALYs (Table 9). However, the underestimation may also be reflected in the source from TA716 as comparator sources were also not from MSI-H/dMMR selected sources (as repeatedly stated in that submission) and the comparator source of utility weight is the same unselected source (Grothey et al. 2013) but have applied even higher utilities than that applied in the base-case of this submission (from TA716 company submission: PFS utility of 0.75 and PPS utility of 0.69).

Further evidence that comparator HRQL may be overestimated can be seen in the gastric tumour site where the CS economic model predict total QALYs of 0.55 for paclitaxel versus 0.39 total QALYs reported in TA378 for docetaxel. This suggests that our economic model may overestimate this comparator outcome by as much as 41% versus results reported in this previous submission.

Validation and transparency

B 29. Priority question: Please provide cross validations, i.e. comparisons,

a) with relevant NICE TAs focussed on other basket trial evaluations, such as for example TA630 and TA644, and elaborate on the identified differences regarding the approach to aggregation and analysis of different tumour sites and supporting assumptions and their effect on estimated (disaggregated) outcomes.

b) with relevant NICE TAs in the related disease areas (tumour sites) and elaborate on the identified differences input parameters, model structure and assumptions and their impact on estimated (disaggregated) outcomes.

The key differences and similarities between the NTRK fusion solid tumour appraisals (relevant pivotal trials and modelling approaches) and this appraisal are summarised below.

KEYNOTE-158 can be considered a basket trial in-line with the pivotal trials in the NTRK appraisals because both fit the broad definition given, for example, in the Histology independent HTA report: “Master protocols are used to evaluate multiple drugs and/or multiple cancer subpopulations in parallel, using a single protocol. Basket trials are used to evaluate a single investigational drug or drug combination in different populations (defined by disease stage, histology or treatment history) and are usually designed as single-arm activity-estimating trials with overall response rate (ORR) as the primary endpoint.”

However, the expected license for pembrolizumab in this indication will not conform with the definition of a “tumour agnostic” indication, in that the license will only include the 5 tumour sites contained in the two pivotal trials; this contrasts with the

NTRK appraisals and respective trials whereby approvals included tumour sites not contained in clinical evidence.

Pivotal trials in both cases were single arm and so external data was required to inform comparator effectiveness. In both NTRK appraisals company submissions involved pooling historical comparator efficacy sources (usually based on previous appraisals) in an ad hoc manner to produce combined comparator efficacy (weighted by tumour site prevalence) and utility and costs also weighted by the same proportions. In this way only a single ICER was produced, in contrast to the approach in this appraisal where results can be assessed by individual pairwise comparisons, weighted in tumour sites or weighted overall for full transparency.

NTRK submissions assumed complete homogeneity in response and efficacy across tumour sites and only one ICER was calculated. This contrasts with the approach here, where total homogeneity is never assumed (i.e., pembrolizumab KM curves for all five tumour sites are never combined/pooled in an analysis). AEGs in either of the NTRK appraisals did not have access to time-to-event outcomes (PFS/OS KM data) by tumour site and so could not apply a BHM framework to these outcomes directly (see response to question B6). However, the AEGs did fit BHM models based on response by tumour site and used these to weight overall (i.e., tumour agnostic) PFS/OS curves.

Model structures employed were not dissimilar only to the extent the conventional 3-state model was used. A full input by input comparison does not seem relevant given that only the Cholangiocarcinoma site seems to be shared (and in addition CRC in the Entrectinib appraisal) and particularly because the populations as well as line (the NTRK appraisals tend to be the very last line) differ considerably.

Therefore, the approach taken in this appraisal is less uncertain in terms of trial data available vs. tumour sites included in the license; pivotal trial data available by tumour site and used in modelling; and exploration of assumptions concerning heterogeneity (no strict homogeneity scenario is presented).

B 30. Priority question: Further external validation of modelled effectiveness would be desirable.

a) **Please report on the face validity assessment (by clinical and health economic experts) of the model structure, model assumptions, model inputs especially relative effectiveness, intermediate outcomes as well as final outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).**

b) **Please provide external validation against alternative data sources, specifically where the MSI-H/dMMR status is known, per tumour site, e.g. KEYNOTE-061 for gastric tumours.**

Model functionality checks were undertaken as described in B.3.14 of Document B and validation of external pembrolizumab sources was also undertaken. In terms of validation compared with the very small MSI-H cohort from the pembrolizumab arm of KEYNOTE-061, see the responses to A32 and A41.

A review by an external health economics professor was undertaken on an earlier version of the technical report for the core global version of the model. These insights were used to adapt the model and applied statistics for the NICE submission and can be summarised as follows:

- Flagged the standard critique for partitioned survival models (i.e., only implicitly model the PD to death movement) however accepted that data limitations are an issue.
- General concerns about applying a BHM to absolute pembrolizumab efficacy outcomes when applying to relative effects (i.e., covariate for treatment) is always preferred. However, accepted that given the 1-arm nature of trials this is hard to avoid and would require similar assumptions to ITCs/MAICs.
- Advised against using pembrolizumab non-responders as proxy for comparator analysis (but worth exploring as scenario analyses).
- A preference for individual PSM models for comparators vs ITC/MAICs but should assess proportional hazards assumptions.
- BHM can provide poor fits in some cases so advised to explore alternative methods (piecewise models and standard parametric modelling).

As already stated, the ad-board was also attended by a different health economics professor and the various insights have been added to document B and influenced the base-case and scenario analyses presented, insights can be summarised as follows:

- Emphasised the novelty of applying BHMs to time-to-event outcomes and compared with NTRK appraisals which could not apply these.
- Sceptical of BHM models unless they produce very different outcomes to standard parametric curves (suggest not much information is being shared between sites anyway if results similar). If very different to PSM approach can imply oversharing between sites, however less likely if non-informative standard priors are used in the Bayesian model (as they are).
- Should not assume complete homogeneity as this assumption is too strong - scenarios that treat CRC as independent from other sites should be tested in scenario analyses.
- Should be careful about excessive waning for immunotherapy efficacy given that the data for these often show long tails and post progression survival after treatment.
- Using trial as source for subsequent treatments is reasonable.
- TTD utility approach is particularly suited to immunotherapies and will bring out benefits of longer post progression survival.
- NICE will expect scenarios with testing in some of the sites.

B 31. The company note that the TECH-VER checklist was completed as part of the in-house quality-control check. Please provide the results of this quality-control check (at least the TECH-VER).

The CS stated that all checks listed in the published TechVER checklist were included in the QC check that was performed. Checks from the TechVER checklist as well as checks from other published sources (Drummond, Phillips) and additional

checks developed internally are included in the proprietary checklist. The checklist is an internal document and intended for use model developers.

Section C: Textual clarification and additional points

C 1. The EAG noted that the PDF provided in the reference pack for Document B reference 25, did not appear to match the title used in the reference list. Whilst the URL does lead to the NICE webpage for TA857, the title and project number in reference 25 appears to refer to the earlier project title used in the committee papers and not the final published guidance.

- Original CS reference 25. National Institute for Health and Care Excellence (NICE). Nivolumab in combination with chemotherapy for untreated advanced gastric or gastro-oesophageal junction cancer [ID1465]. In development [GID-TA10352]. 2020 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10352/

- Document in the reference pack: National Institute for Health and Care Excellence (NICE). Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro oesophageal junction or oesophageal adenocarcinoma: NICE technology appraisal guidance 857. 2023. Available from: https://www.nice.org.uk/guidance/ta857

Please confirm which NICE document should be cited.

The discrepancy is due to final guidance (TA857) being published in the interim and the latter document refers to this, whereas the original reference is related to the same appraisal while it was still ongoing (ID1465]; however the source appraisal is the same in either case as shown by the link.

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Please note that pdfs of relevant publications are not included in current reference pack if they were already provided with the company submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Patient Organisation Submission

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

1.Your name	[redacted]
2. Name of organisation	AMMF – The Cholangiocarcinoma Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	AMMF is a charity, registered with the Charity Commission for England and Wales, registration no 1091915. It is the UK's only charity dedicated solely to cholangiocarcinoma (CCA). Funding is received via donations from members of the public, and some industry funding is received by way of sponsorship for projects such as our annual CCA conference. The charity does not have members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	N/A

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?	AMMF supports patients with cholangiocarcinoma and their caregivers, providing them with information on treatments and clinical trials. We communicate with patients and their loved ones on a one to one basis by email and telephone, and face to face at our annual conference, and many patients and carers use AMMF's private online discussion forums to discuss their treatments and participation in clinical trials www.ammf.org.uk

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?	The symptoms of cholangiocarcinoma (CCA) can be vague and easily attributed to a number of other causes and because of this, together with a lack of awareness at primary care level, this cancer is frequently diagnosed late. For the majority of patients, this late diagnosis will mean their cancer is inoperable and for them, this is a terminal diagnosis. For many patients this diagnosis and the prognosis can be truly shocking and they find it very difficult to assimilate the details. Patients struggle to accept that there really is so little treatment available to them, and that a diagnosis of inoperable CCA means their life will end soon – they have very little time left. Currently a resection is the only potentially curative treatment there is for CCA, so inoperable patients are left with very limited options. The standard first line treatment for those with inoperable CCA is the chemotherapy combination, Gemcitabine and Cisplatin. Undergoing this chemotherapy, which might or might not extend their life for a few months[1], is often at the expense of the quality of their life, and that of their families. For carers, understanding the diagnosis and its implications can be as difficult for them as for the patient. Many struggle to comprehend that there is no effective treatment for their loved one, and ask AMMF for advice on, 'treatments not available under the NHS'. Seeing loved ones enduring the side effects of chemotherapy, including repeated infections requiring hospitalisation which takes them away from their families when their life expectancy is so short, is very difficult. As is, of course, trying to come to terms to what is happening, not only to their loved one, but to their lives in general – especially as so many are in what should be the 'prime of their life'. Although CCA is considered a cancer affecting older people, at AMMF we hear from many in their 30s, 40s and up with this diagnosis. When the survival rates are improving and more effective treatments are being discovered for many other cancers, a diagnosis of cholangiocarcinoma, and learning that there is so little in the treatment armoury, leaves people – patients and carers - feeling confused, isolated and helpless. Many of the comments we receive at AMMF are, sadly, similar: "After my diagnosis I felt so alone and afraid, I had no one to turn to for help." "I was shell shocked. I didn't know who to turn to for help. I was alone."

	"I went through endless tests; the doctors didn't know what was wrong with me. I lost valuable time." "They told me surgery was my only chance of survival, but it might already be too late." *[1]ABC-02 trial 2010: "The median survival in the cisplatin–gemcitabine group was 11.7 months (95% confidence interval [CI], 9.5 to 14.3), as compared with 8.1 months (95% CI, 7.1 to 8.7) for the gemcitabine-only group (P<0.001)."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	With the advent of molecular profiling, targeted therapies and immunotherapies - one approved by NICE and others still under clinical study – all CCA patients should be able to access molecular profiling but still find this difficult under the NHS, which means they may miss out on therapies that could extend their lives. They also see other therapies, for example other targeted therapies, immunotherapies, and SIRT, available to CCA patients in other countries, and they find it very difficult to understand why these effective treatments (not curative, but life extending) are not available for cholangiocarcinoma patients within the NHS. Many will search for treatments available privately or internationally.

8. Is there an unmet need for patients with this condition?	There are a number of unmet needs for cholangiocarcinoma patients: Effective treatments for CCA are desperately needed. The incidence of this disease is increasing year on year, with mortality mirroring incidence[2], and many younger adults being diagnosed. Currently resection is the only potentially curative treatment, but few are eligible for this. Standard of care 1st line chemotherapy for inoperable CCA patients hasn't changed in years and offers modest, if any, benefit. Currently there is one approved targeted therapy. New and more effective treatments for CCA are desperately needed. Centres of Expertise for CCA patients are needed There seems to be no set pathway/guidance for the care of cholangiocarcinoma patients, many are never seen by those with specialist knowledge, and many are not considered for surgery nor for clinical trials. AMMF strongly believes that all CCA patients should be seen in 'centres of expertise' for confirmation of their diagnosis (operable/inoperable), and where their treatment pathway should be endorsed by an HPB multidisciplinary team, experienced in the care of CCA patients. Molecular profiling is needed for all CCA patients Molecular profiling should now be available for all those diagnosed with CCA – at diagnosis or during 1st line treatment. With the advent of targeted therapies and immunotherapies such as pembrolizumab which is effective for those with high microsatellite instability or mismatch repair deficiency, this is essential so that all those eligible for such treatments can be considered in a timely manner. Currently it seems molecular profiling under the NHS is available to only very few CCA patients in the UK, with many seeking this privately. [2]*Incidence and Mortality rates of cholangiocarcinoma in England* *https://www.annalsofoncology.org/article/S0923-7534(19)30962-7/fulltext*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and carers look to new technologies and therapies with the hope these will offer extended survival over the more standard chemotherapies and/or best supportive care that might be offered. Although pembrolizumab is effective only for those few with high microsatellite instability or mismatch repair deficiency cancer, for them this treatment is something they know should be effective in extending survival, more so than further chemotherapy, which might or might not be effective for them, or best supportive care.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients and carers see new technologies heralding new hope – the only disadvantages expressed by patients and carers that AMMF is aware of is that clinical trials are available to so few, and similarly that new technology and therapies are not adopted in a timely and uniform manner.

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.	Pembrolizumab is effective for those with high microsatellite instability or mismatch repair deficiency cancer. Those CCA patients without microsatellite instability high or mismatch repair deficient cancers will not benefit from this treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Incidence of CCA in increasing, with mortality that parallels incidence. • Currently there is very little effective treatment for CCA patients. • Many CCA patients are not considered for surgery nor for clinical trials – 'centres of expertise' are needed for confirmation of diagnosis and treatment pathway, and for molecular profiling. • All CCA patients should receive molecular profiling at diagnosis or during 1st line treatment • For those few found to have microsatellite instability high or mismatch repair deficient cancers, pembrolizumab offers a realistic treatment, extending survival with good quality of life.

Thank you for your time.

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Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Center+ (UMC+)

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Date completed 22/03/2023

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number STA 13/57/86.

Declared competing interests of the authors None.

Acknowledgements

We gratefully acknowledge the expert advice input from Veerle Coupe, Department of Epidemiology and Data Science, Amsterdam Public Health, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, the Netherlands.

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This report should be referenced as follows:

Wolff R, Witlox W, Grimm S, Sugden B, Abu-Zarah T, Otten T, Perry M, Patel M, Noake C, Armstrong N, Joore M. Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2023.

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Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Sabine Grimm, Bradley Sugden, Teebah Abu-Zarah, Thomas Otten, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mark Perry and Mubarak Patel acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance.

Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
aEC	Advanced endometrial cancer
AEOSI	Adverse Event of Special Interest
AiC	Academic in Confidence
AIC	Akaike Information Criterion
Anti-PD-1	Anti programmed death 1
ASaT	All subjects as treated
ASC	Active symptom control
ASCO	American Society of Clinical Oncology
BHM	Bayesian hierarchical model
BIC	Bayesian information criterion
BRAF	Gene that encodes the B-Raf protein
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPOX	Oxaliplatin + capecitabine
CEA	Cost-effectiveness analysis
CI	Confidence interval
CiC	Commercial in Confidence
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRD	Centre for Reviews and Dissemination
CS	Company submission
CTCAE	Common Terminology Criteria for Adverse Events
DAE	Discontinuation due to adverse event
DALY	Disability-adjusted life year
DCR	Disease control rate
DIC	Deviance Information Criterion
dMMR	DNA mismatch repair deficient
DNA	Deoxyribonucleic acid
DOR	Duration of response
DR	Date range
DSU	Decision Support Unit
EAG	Evidence Assessment Group
ECI	Event of clinical interest
ECM	Established clinical management
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC	European Organisation for the Research and Treatment of Cancer
QLQ-C30	Quality of Life Questionnaire C30
EQ-5D	EuroQol 5D Quality of Life Instrument
ESMO	European Society of Medical Oncology
ESS	Effective sample size
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixing errors
FOLFIRI	Folinic acid, fluorouracil, irinotecan
FOLFOX	Folinic acid, fluorouracil, oxaliplatin
FOLFOXIRI	Folinic acid, fluorouracil, irinotecan, oxaliplatin

FV	Fixing violations
G-CSF	Granulocyte colony-stimulating factor
h	Hour
HCRU	Health care resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HTAD	Health Technology Assessment Database
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
iNHB	Incremental net health benefit
IPD	Individual participant data
IRC	Independent Radiologist Review Committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
KRAS	Kirsten rat sarcoma virus gene
KSR	Kleijnen Systematic Reviews Ltd
LY	Life year
mAB	Monoclonal antibody
MAIC	Matching-adjusted indirect comparison
mCRC	Metastatic colorectal cancer
MeSH	Medical Subject Heading
mFOLFIRI	Modified folinic acid, fluorouracil, irinotecan
mFOLFOX	Modified folinic acid, fluorouracil, oxaliplatin
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MJ	Matters of judgement
MMR	Mismatched repair
MSD	Merck Sharp and Dohme
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
NA	Not applicable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Non-estimable
NL	The Netherlands
NR	Not reached
NRAS	Enzyme encoded by the NRAS gene
NTRK	Neurotrophin receptor tyrosine kinase
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PF	Progression-free
PFS	Progression-free survival
pMMR	Proficient mismatch repair

PPP	Platinum pre-treated population
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q3W	Once every three weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RAS	Rat sarcoma virus
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SD	Search date
SD	Stable disease
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SoC	Standard of care
STA	Single Technology Appraisal
STM	State transmission models
TA	Technology Appraisal
TAS-102	Tipiracil hydrochloride
ToT	Time on treatment
TPC	Treatment of physician's choice
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTP	Time to progression
UK	United Kingdom
UMC+	University Medical Center+
US	United States
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WES	Whole exome sequencing
XELOX	Capecitabine plus oxaliplatin

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 relates to the clinical effectiveness, and Section 1.5 relates to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Section
1	Inappropriate exclusion of comparators from the company decision problem.	2.3
2	External validity of the trial evidence to the UK target population.	3.2.3.2
3	Adverse event data for KEYNOTE-158 were aggregated, and not presented for each separate tumour site.	3.2.7.1
4	Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population.	3.4.3
5	High risk of bias in comparative efficacy.	3.4
6	Populations were aggregated across all tumour sites based on their MSI-H/dMMR status. However, MSI-H/dMMR status for most comparators was unknown and heterogeneity between tumour sites seems substantial.	4.2.2
7	Treatment baskets were used to inform SoC per tumour site, which may bias the costs and outcomes of SoC in the economic model.	4.2.4
8	The selection of patients in the comparator studies was not based on their MSI-H/dMMR status, which introduced (methodological) uncertainty in the estimation the relative effectiveness of pembrolizumab.	4.2.6
9	The suitability of the Bayesian hierarchical model approach in the context of this submission was questionable.	4.2.6
10	The time-to-death utility approach to model the HRQoL of tumour sites included in KEYNOTE-158 was questionable.	4.2.8
11	Assumptions regarding the modelling of subsequent treatments were questionable.	4.2.9
12	Testing costs to identify patients with MSI-H/dMMR were not included in the company's base-case analysis.	4.2.9
13	Severity estimates were based on the company's modelling of QALYs, which was subject to limitations, and therefore uncertain.	4.2.10
14	The majority of the company's scenario analyses could not be reproduced and lacked face validity.	5.2

dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; MSI-H = microsatellite instability-high; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year; SoC = standard of care; TSD = Technical Support Document; UK = United Kingdom

1.2 Overview of key model outcomes

National Institute for Health and Care Excellence technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) 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:

- Increased progression-free survival (PFS) for pembrolizumab in the colorectal cancer (CRC) indication (QALYs in the progression-free (PF) health state increased by [redacted] [redacted] of total QALYs] compared with standard of care (SoC)) and increased time-to-death in the other indications (QALYs in time to treatment discontinuation (TTD) 360+ days increased by [redacted] [redacted] of total QALYs]).
- Increased overall survival (OS) for pembrolizumab (survival increased by [redacted] years compared with SoC).

Overall, the technology is modelled to affect costs by:

- The higher treatment costs (additional costs of [redacted] compared with SoC).
- The higher resource use costs (additional costs of [redacted] compared with SoC).

The modelling assumptions that have the greatest effect on the overall indication net health benefit (NHB; based on the company's deterministic sensitivity analyses) were:

- Administration costs of oral chemotherapy
- Proportion of CRC patients receiving subsequent therapy after pembrolizumab
- Utility values by Grothey 2013[1] to inform health-related quality of life (HRQoL) in CRC

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the overall indication NHB were related to:

- Treatment waning
- QALYs and costs discounting
- Survival modelling of OS and PFS in the pembrolizumab arm

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence from certain comparators (Table 1.2).

Table 1.2: Issue 1: Inappropriate exclusion of comparators from the company decision problem

Report Section	**2.3**
Description of issue and why the EAG has identified it as important	Nivolumab + ipilimumab, irinotecan + raltitrexed and ECM were designated as relevant comparators by the NICE scope, but not included in the decision problem. The company presented an argument that nivolumab + ipilimumab would not be an appropriate comparator to pembrolizumab at the second line stage, as nivolumab + ipilimumab would only be used where pembrolizumab had not been used first line, but this is the very population of the decision problem. ECM was listed as a separate comparator in the NICE scope. This raises a question as to what it might entail, given that other treatments were separately listed and that those other treatments could also be regarded as a type of ECM. However, the company did not clear resolve this ambiguity by stating that the comparators that they considered could have been considered as a whole as

Report Section	2.3
	ECM. This then leaves open the possibility that some treatments, which might be regarded as ECM were not considered. Therefore, the company might not have considered all relevant comparators in their analysis of evidence. Failure to consider all these potentially relevant comparators may yield spurious conclusions about pembrolizumab efficacy.
What alternative approach has the EAG suggested?	Inclusion of these comparators in the decision problem, and therefore extending the scope of comparators used in the analyses.
What is the expected effect on the cost effectiveness estimates?	The omission of these comparators may have contributed to a spurious inflation of cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Inclusion of these comparators in the decision problem, and therefore extending the scope of comparators used in the analyses.
EAG = Evidence Assessment Group; ECM = established clinical management; NICE = National Institute for Health and Care Excellence	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified a number of concerns with the evidence presented on the clinical effectiveness, namely the potentially reduced external validity of the trial evidence (see Table 1.3) as well as the aggregation of adverse events (Table 1.4), the mismatch between pembrolizumab and comparators in microsatellite instability-high (MSI-H)/deoxyribonucleic acid (DNA) mismatch repair deficient (dMMR) status (Table 1.5) and the lack of transparency in the derivation of comparator data used for the health economic analysis (Table 1.6).

Table 1.3: Issue 2: External validity of the trial evidence to the UK target population

Report Section	3.2.3.2
Description of issue and why the EAG has identified it as important	For colorectal and gastric cancer, and to a lesser extent small intestine cancer, the EAG notes large differences in ethnicity between the trials and the UK data provided by the company. The UK data are not specifically in people with MSI-H/dMMR, and the EAG recognises that it is possible that the ethnic proportions in a more relevant UK subgroup with MSI-H/dMMR status might be more closely aligned with the trial data (which is in an MSI-H/dMMR population). However, given evidence that ethnicity is not strongly linked to MSI-H/dMMR status, it is unlikely that the ethnic make-up of a UK MSI-H/dMMR subgroup would be appreciably different to the ethnic make-up of the UK data presented by the company. Given that the UK data may reflect the ethnic proportions of the specific UK target population, there are possible discrepancies between the trial data and the UK target population.
What alternative approach has the EAG suggested?	A subgroup analysis for ethnicity might demonstrate if ethnicity is an effect modifier. If it is, then the possible discrepancies in ethnicity between trial and UK target population may reduce the applicability of trial findings.
What is the expected effect on the cost effectiveness estimates?	Unknown. This will depend on the effect of ethnicity on outcomes.
What additional evidence or analyses might help to resolve this key issue?	A subgroup analysis for ethnicity might demonstrate if ethnicity is an effect modifier. If it is, then the possible discrepancies in

Report Section	3.2.3.2
	ethnicity between trial and UK target population may reduce the applicability of trial findings.
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; MSI-H = microsatellite instability-high; UK = United Kingdom	

Table 1.4: Issue 3: Aggregation of AE data for KEYNOTE-158

Report Section	3.2.7.1
Description of issue and why the EAG has identified it as important	Aggregation of data were not performed for the clinical efficacy outcomes from KEYNOTE-158, but the four tumour sites were combined for appraisal of AEs. It is possible that an aggregated result could obscure high levels of AEs in a single tumour site
What alternative approach has the EAG suggested?	Subgrouping of the aggregated data is required.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Subgrouping of the aggregated data and comparative analysis of these sub-grouped data.
AE = adverse event; EAG = Evidence Assessment Group	

Table 1.5: Issue 4: Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population

Report Section	3.4.3
Description of issue and why the EAG has identified it as important	The ITC uses pembrolizumab trials in the MSI-H/dMMR population and comparator trials that are *not* in the MSI-H/dMMR population. However, MSI-H/dMMR may be a treatement effect modifier. The company provided evidence that suggested MSI-H/dMMR status may worsen prognosis. This suggests that the mismatch might have a conservative effect, i.e., it may reduce rather than enhance apparent pembrolizumab effectiveness. However, the company also cites clinical opinion suggesting that MSI-H/dMMR status may improve the effectiveness of immunotherapy treatment. This additional effect may increase uncertainty of the magnitude and direction of any effect modification.
What alternative approach has the EAG suggested?	The EAG has suggested that pembrolizumab data in people *without* MSI-H/dMMR status be compared to the non-MSI-H/dMMR comparator data. This may have disadvantages in terms of reduced external validity, but the advantages in terms of enhanced internal validity may be greater.
What is the expected effect on the cost effectiveness estimates?	There is the potential for the cost effectiveness to have been spuriously increased by the mismatch.
What additional evidence or analyses might help to resolve this key issue?	The EAG has suggested that pembrolizumab data in people *without* MSI-H/dMMR status be compared to the non-MSI-H/dMMR comparator data. This may have disadvantages in terms of reduced external validity, but the advantages in terms of enhanced internal validity may be greater.
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; MSI-H = microsatellite instability-high	

Table 1.6: Issue 5: High risk of bias in comparative efficacy

Report Section	3.4.3
Description of issue and why the EAG has identified it as important	Having presented the ITC and MAIC evidence, with its limitations as described above, the company concludes that the ITC and MAIC evidence is not fit for purpose for the economic analysis, and that the health economic strategy will therefore be based upon the following approach: *"parametric survival distributions were fitted to the comparator pseudo-IPD with the most clinically plausible extrapolation chosen for use in the base case"*. The EAG agree that all methods are limited, including the non-responder-based analysis, as acknowledged by the company. However, although the base case method has the advantage of not assuming proportional hazards, it still uses non-randomised controlled data with no adjustment for confounding. Therefore, all methods imply a high risk of bias in comparative efficacy for pembrolizumab in all cancers.
What alternative approach has the EAG suggested?	Given the serious limitations of all approaches, there seems to be little that can be suggested to reduce the risk of bias.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Given the serious limitations of all methods of survival estimation, the EAG suggests the use of external validation and clinical expert opinion to test the independently fitted parametric survival curves, alongside other criteria, in line with TSD 14 (see key issue 8).
EAG = Evidence Assessment Group; IPD = individual participant data; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; TSD = technical support document	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The main EAG results are reproduced using confidential patient access schemes in a confidential appendix. The key issues in the cost effectiveness evidence are discussed in the issue Tables below.

Table 1.7: Issue 6: Model structure – Aggregating tumour sites results

Report Section	4.2.2
Description of issue and why the EAG has identified it as important	The company aggregated populations across all tumour sites based on their MSI-H/dMMR status to generate outcomes for the overall indication. However, MSI-H/dMMR status for most comparators was unknown and heterogeneity between tumour sites seems substantial.
What alternative approach has the EAG suggested?	Further justification, supported by evidence, as to the appropriateness of aggregating results across tumour sites.
What is the expected effect on the cost effectiveness estimates?	The impact on cost effectiveness results (direction of influence and magnitude) differs per tumour site.
What additional evidence or analyses might help to resolve this key issue?	Further justification, supported by evidence, as to the appropriateness of aggregating results across tumour sites.
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; MSI-H = microsatellite instability-high	

Table 1.8: Issue 7: Intervention and comparators – Treatment baskets to inform SoC

Report Section	4.2.4
Description of issue and why the EAG has identified it as important	Treatment baskets were used to inform SoC per tumour site, comprising a mixture of single comparators and pooled comparators. The comparator effectiveness and costs are therefore based on the average clinical effectiveness and weighted average costs across the treatments included in the comparator basket which may bias the costs and outcomes of SoC in the economic model.
What alternative approach has the EAG suggested?	The EAG presented fully incremental analyses results per tumour site. Present fully incremental analysis results moving forward.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	NA
EAG = Evidence Assessment Group; NA = not applicable; SoC = standard of care	

Table 1.9: Issue 8: Treatment effectiveness and extrapolation – Methodology for estimation of relative effectiveness

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Except for paclitaxel in gastric cancer and paclitaxel/doxorubicin in endometrial cancer, the selection of patients in the comparator studies was not based on their MSI-H/dMMR status. This introduced uncertainty in the estimation the relative effectiveness of pembrolizumab. There is methodological uncertainty about how to best analyse the data.
What alternative approach has the EAG suggested?	A non-responder scenario analysis, assuming that patients treated with pembrolizumab from KEYNOTE-158 and KEYNOTE-164 who do not achieve a partial or complete response have survival outcomes (OS and PFS) that are consistent with patients who received a comparator treatment within established clinical practice.
What is the expected effect on the cost effectiveness estimates?	The scenario analysis resulted in an increased ICER.
What additional evidence or analyses might help to resolve this key issue?	Full NICE DSU TSD 14 and 21 details that support the optimal parametric curves to extrapolate the non-responder OS and PFS KM data. Provide further details on the implementation of the non-responder analysis into the economic model and elaborate on how this analysis also affects the modelled pembrolizumab life years and QALY gains.
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; DSU = Decision Support Unit; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; MSI-H = microsatellite instability-high; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TSD = Technical Support Document	

Table 1.10: Issue 9: Treatment effectiveness and extrapolation – BHM approach for modelling of pembrolizumab OS and PFS

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG questions the suitability of the BHM approach in the context of this submission. The BHM approach would only be appropriate if the assumption that the different tumour sites can be considered subgroups of an overarching MSI-H/dMMR solid tumour population is justified.
What alternative approach has the EAG suggested?	Apply the BHM approach only to comparable tumour sites, justified and supported by clinical arguments and evidence rather than statistical arguments. Modelling the KEYNOTE-164 data for the colorectal cancer (CRC) tumour site separately and applying the BHM approach only to the tumour sites included in the KEYNOTE-158 basket trial. Provide further justification on the use of a BHM approach for time-to-event outcomes rather than response outcomes.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Apply the BHM approach only to comparable tumour sites, justified and supported by clinical arguments and evidence rather than statistical arguments. Modelling the KEYNOTE-164 data for the CRC tumour site separately and applying the BHM approach only to the tumour sites included in the KEYNOTE-158 basket trial. Further elaboration on the suitability of the BHM approach for time-to-event outcomes rather than response outcomes.
BHM = Bayesian hierarchical modelling; CRC = colorectal cancer; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; MSI-H = microsatellite instability-high	

Table 1.11: Issue 10: Health-related quality of life - Time-to-death approach for modelling the HRQoL of tumour sites in KEYNOTE-158

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The company used a time-to-death utility approach to model the HRQoL of tumour sites included in KEYNOTE-158. The EAG questioned this, as it is not part of the NICE DSU TSD guidance on utilities and lacks details on statistical analyses, it seems inconsistent with the progression-based model structure, and it lacks face validity.
What alternative approach has the EAG suggested?	The EAG uses the more conservative health state-based approach of modelling utilities as a function of progression status in its base-case.
What is the expected effect on the cost effectiveness estimates?	Using the health state-based approach of modelling utilities increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	Provide full details of the statistical analyses for the various models that were considered.
DSU = Decision Support Unit; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; TSD = Technical Support Document	

Table 1.12: Issue 11: Resources and costs – Modelling of subsequent treatments

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	The EAG questions the assumptions that (1) the proportions of patients receiving subsequent treatments are equal regardless of initial treatment and that (2) the modelled subsequent treatments are reflective of UK clinical practice.
What alternative approach has the EAG suggested?	Further evidence and justification to support these assumptions.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Further evidence and justification to support these assumptions.
EAG = Evidence Assessment Group; UK = United Kingdom	

Table 1.13: Issue 12: Resources and costs - Testing costs to identify patients with MSI-H/dMMR

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	The company did not include testing costs to identify patients with MSI-H/dMMR in their base-case analysis.
What alternative approach has the EAG suggested?	The EAG adopted the company's scenario analysis including testing costs in its base-case.
What is the expected effect on the cost effectiveness estimates?	The inclusion of testing costs slightly increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	Evidence to support the assumptions that 1) testing in colorectal cancer (CRC) and endometrial cancer is routinely commissioned in the NHS, and 2) 50% of patients of the remaining tumour sites already receive these tests.
CRC = colorectal cancer; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; MSI-H = microsatellite instability-high; NHS = National Health Service	

Table 1.14: Issue 13: Severity – Approach for estimation of severity

Report Section	4.2.10
Description of issue and why the EAG has identified it as important	Severity estimates are based on the company's modelling of QALYs, which is subject to limitations in the data used, and therefore uncertain. The company's time-to-death approach to estimating HRQoL leads to a [redacted] QALY multiplier for two tumour sites (gastric and small intestine) than the alternative, more conventional health state (progression-) based approach to modelling HRQoL.
What alternative approach has the EAG suggested?	Use the health state (progression-) based approach to modelling HRQoL.
What is the expected effect on the cost effectiveness estimates?	ICERs will [redacted] with the alternative approach suggested by the EAG.
What additional evidence or analyses	QALY estimates from NICE TAs in populations with MSI-H/dMMR status.

Report Section	4.2.10
might help to resolve this key issue?	
dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; MSI-H = microsatellite instability-high; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year; TA = technology appraisal	

Table 1.15: Issue 14: Reproducibility and face validity of scenario analyses

Report Section	5.2
Description of issue and why the EAG has identified it as important	The EAG was unable to reproduce the majority of the scenario analyses reported in Table 93 of the CS. The results of some scenario's (e.g., pembrolizumab OS, PFS – BHM Weibull) also lacked face validity, i.e., the EAG found an increased NHB compared to the company's base-case while the company reported a decreased NHB in CS, Table 93.
What alternative approach has the EAG suggested?	Further justification for the differences between the EAG and company scenario analyses and the lack of face validity should be provided. In addition, step by step details should be provided on how the company's scenario analyses can be reproduced in the economic model.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Further justification for the lack of reproducibility and face validity of the company's scenario analyses should be provided. In addition, step by step details should be provided on how the company's scenario analyses can be reproduced in the economic model.
BHM = Bayesian hierarchical modelling; CS = company submission; EAG = Evidence Assessment Group; NHB = net health benefit; OS = overall survival; PFS = progression-free survival	

1.6 Other key issues: summary of the EAG's view

There were no other key issues.

1.7 Summary of the EAG's view

The CS base-case ICER (probabilistic) for the overall indication was £12,637 per QALY gained (Table 1.16). The estimated EAG base-case ICER (probabilistic) for the overall indication, based on the EAG preferred assumptions highlighted in Section 6.1, was £16,531 per QALY gained. The estimated deterministic base-case ICERs (based on a fully incremental analysis per tumour site) for colorectal cancer, endometrial cancer, gastric cancer, small intestine cancer and cholangiocarcinoma were £13,845, £17,785, £27,387, £21,970, and £15,250 per QALY gained, respectively. The most influential adjustments were the 1.2 QALY multipliers for tumour sites except cholangiocarcinoma, and the health state-based approach to estimate utility values. The ICER increased most in the scenario analysis using a non-responder analysis to estimate the relative effectiveness of pembrolizumab.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of pembrolizumab, which can be partly resolved by the company by conducting further analyses. This includes providing an estimation of the OS and PFS relative effectiveness of pembrolizumab in patients that all had a positive MSI-H/dMMR status, an analysis applying the Bayesian hierarchical model (BHM) approach only to comparable tumour sites based on clinical arguments and evidence, full details of the statistical analyses for the various time-to-death models that were considered for the estimation of HRQoL, further justification for assumptions made regarding the modelling of subsequent

treatments and costs for MSI-H/dMMR testing, and further justification for the lack of reproducibility and face validity of scenario analyses. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of pembrolizumab compared with relevant comparators.

Table 1.16: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
CS base-case						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,759	[redacted]	[redacted]	[redacted]	£12,796	1.85
Matter of judgement (1-Tumour site distribution based on UK epidemiological data)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£32,561	[redacted]	[redacted]	[redacted]	£13,415	1.78
Matter of judgement (2-Health state-based approach to estimate utility values)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,759	[redacted]	[redacted]	[redacted]	£13,744	1.63
Matter of judgement (3-Inclusion of MSI-H/dMMR testing costs)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,759	[redacted]	[redacted]	[redacted]	£12,987	1.83
Matter of judgement (4-1.2 QALY multipliers for tumour sites except cholangiocarcinoma)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,759	[redacted]	[redacted]	[redacted]	£13,974	1.58
Deterministic EAG base-case						
Pembrolizumab	[redacted]	[redacted]				
SoC	£32,561	[redacted]	[redacted]	[redacted]	£16,856	1.14
Probabilistic EAG base-case						
Pembrolizumab	[redacted]	[redacted]				
SoC	£33,138	[redacted]	[redacted]	[redacted]	£16,531	1.20
Scenario analysis (5-Non-responder analysis)						
Pembrolizumab	[redacted]	[redacted]				
SoC	£36,020	[redacted]	[redacted]	[redacted]	£20.336	0.72

[1]iNHB for willingness-to-pay of £30,000 per QALY
CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; MSI-H = microsatellite instability-high; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	• Adults with unresectable or metastatic MSI-H or dMMR CRC previously treated with fluoropyrimidine-based combination therapy. • Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation. • Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy.	• Adults with unresectable or metastatic MSI-H or dMMR CRC previously treated with fluoropyrimidine-based combination therapy. • Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation. • Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy	In line with final NICE scope	No comment
Intervention	Pembrolizumab	Pembrolizumab	In line with final NICE scope	No comment
Comparator(s)	For people with previously treated MSI-H or dMMR with unresectable or metastatic CRC:	For people with previously treated MSI-H or dMMR with	*For people with previously*	The rationale for not using

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	• Established management without pembrolizumab • Nivolumab with ipilimumab • Single-agent irinotecan (after FOLFOX) • FOLFIRI (after either FOLFOX or CAPOX) • Raltitrexed (if 5-fluorouracil and folinic acid are not suitable) • Trifluridine-tipiracil For people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer: • Established management without pembrolizumab • Chemotherapy, including: • Carboplatin and paclitaxel • Paclitaxel monotherapy • Doxorubicin monotherapy • Carboplatin monotherapy • Hormone therapy (such as medroxyprogesterone acetate and megestrol) For people with previously treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine, or biliary cancer: • Established management without pembrolizumab	unresectable or metastatic CRC: • FOLFIRI/FOLFOX/FOLFO 4/ mFOLFOX6 (70% of eligible patients) • Trifluridine-tipiracil (30% of eligible patients For people with previously treated MSI-H or dMMR with advanced or recurrent endometrial cancer: • Chemotherapy, including paclitaxel, doxorubicin and carboplatin For people with previously treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine and biliary cancer: *Gastric cancer* • Paclitaxel • FOLFIRI *Small intestine cancer* • FOLFIRI/FOLFOX *Biliary cancer* • FOLFOX • FOLFIRI	*treated MSI-H or dMMR with unresectable or metastatic colorectal cancer:* Single-agent irinotecan and raltitrexed are not considered relevant comparators in this appraisal as clinical expert opinion confirmed that they are not routinely used in clinical practice unless other treatments are contra-indicated. Nivolumab with ipilimumab is not considered a relevant comparator in this appraisal. Given that nivolumab with	nivolumab with ipilimumab as a comparator in the decision problem (for the sub-population with CRC) is not clearly explained, despite this comparator being requested in the NICE scope. The rationale for not using single-agent irinotecan and raltitrexed as a comparator in the decision problem (for the sub-population with CRC), which was requested in the NICE scope, is based on clinical opinion that this agent is

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			ipilimumab cannot be used to treat patients who received any prior treatment with an anti-PD-1 antibody, and pembrolizumab is the SoC for patients with untreated metastatic CRC with MSI-H or dMMR, nivolumab with ipilimumab will be the treatment of choice for a small subset of people who receive fluoro-pyrimidine-based combination chemotherapy in first-line when the MSI-H/dMMR status is not yet confirmed or	rarely prescribed in clinical practice. There is a need for the company back up the rationale with more objective evidence. For the sub-population with endometrial cancer, the decision problem appears sufficiently similar to the NICE scope in terms of chemotherapy. The rationale for excluding hormone therapy appears to be valid. The NICE scope includes 'established management

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			where the progression of the disease requires fast acting chemo-therapy. Clinical expert opinion suggested that these patients will routinely receive nivolumab with ipilimumab unless there are comorbidities. In these instances, which are expected to occur in a small proportion of patients (subset of the subset) pembrolizumab may be a suitable option. *For people with previously treated MSI-H or dMMR with*	without pembrolizumab' as a valid comparator for all three sub-populations (colorectal tumours, endometrial tumours and gastric, biliary, or small intestine tumours). This aspect of the NICE scope implies that any comparator, provided it is currently used in UK clinical practice, is a valid comparator. However, 'established management without pembrolizumab' has not been included in the

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			advanced or recurrent endometrial cancer: Based on clinical expert consultation, SoC is chemotherapy such as paclitaxel, doxorubicin and carboplatin. Hormone therapy is only used with palliative intent if all other treatment options are exhausted, or patients cannot tolerate further lines of chemotherapy which is not the proposed positioning for pembrolizumab. *For people with previously*	decision problem for these three sub-populations. Failure to include this criterion in the decision problem means that the company does not have to consider all relevant comparators in their evidence. If established management options have not been included amongst the specified comparators in the decision problem this will lead to a biased evaluation of the evidence.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			treated MSI-H or dMMR with unresectable or metastatic gastric, small intestine and biliary cancer: Established clinical management without pembrolizumab has been identified based on European guidelines and clinical expert consultation. With regard to small intestine cancer, clinical experts identified FOLFOX/ FOLFIRI as the treatment of choice but did not expect MSD to find any published evidence on	

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			efficacy. This was confirmed in the SLR which only identified evidence for nab-paclitaxel, which is used in the CEA.	
Outcomes	• OS • PFS • RR • DOR • Adverse effects of treatment • HRQoL	• OS • PFS • RR • DOR • Adverse effects of treatment • HRQoL	NA	No comment
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. • 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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account. • The use of pembrolizumab for this indication is conditional on the presence of either MSI-H or dMMR classified tumours. The	Cost effectiveness of the treatments specified are expressed in terms of incremental cost per QALY. The economic analysis implements a lifetime time horizon for estimating clinical and cost effectiveness. Costs are included from an NHS and PSS perspective and use sources reflecting the current prices available to the NICE (with the exception of	Previous appraisals and clinical opinion suggest testing is well established in colorectal and endometrial cancer and so for consistency testing costs are not included in the base-case. However, testing costs for the remaining	Testing costs to identify patients with MSI-H/ dMMR were explored by the company in a scenario analysis, but not included in their base-case. The EAG adopted the company's scenario analysis including

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	economic modelling should include the costs associated with diagnostic testing for MSI-H or dMMR in people with solid tumours who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 4.8 of the Guidance Development Manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introductionto-health-technology-evaluation).	therapies available with a confidential discount). Testing costs are not included in the base-case analysis.	tumour sites are explored in scenario analyses.	testing costs in its base-case.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Tumour site • Previous therapy	Cost effectiveness analysis for each tumour site are provided.	No additional subgroup analysis was performed.	No comments.
Special considerations including issues related to equity or equality		No issues with equity or equality have been identified.		

Based on Table 1 and pages 10 to 12 of the CS[2]
CAPOX = oxaliplatin plus capecitabine; CEA = cost effectiveness analysis; CRC = colorectal cancer; CS = company submission; DOR = duration of response; dMMR = DNA mismatch repair deficient: DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin; HRQoL = health-related quality of life; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; MSD = Merck Sharp and Dohme; MSI-H = microsatellite instability-high; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD-1 = programmed death 1; PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life year; RR = response rate; SLR = systematic literature review; SoC = standard of care; UK = United Kingdom

2.1 Population

The population defined in the scope comprises:

1. Adults with unresectable or metastatic microsatellite instability-high (MSI-H) or deoxyribonucleic acid (DNA) mismatch repair deficient (dMMR) colorectal cancer previously treated with fluoropyrimidine-based combination therapy.
2. Adults with advanced or recurrent MSI-H or dMMR endometrial cancer, whose disease has progressed on or following treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation.
3. Adults with unresectable or metastatic MSI-H or dMMR gastric, small intestine, or biliary cancer, whose disease has progressed on or following at least one prior therapy.

The population in the decision problem is in line with the National Institute for Health and Care Excellence (NICE) scope.

EAG comment: No comment.

2.2 Intervention

The intervention (pembrolizumab) is in line with the scope.

Pembrolizumab (KEYTRUDA®, Merck Sharp and Dohme; MSD) is a humanised monoclonal anti-programmed cell death-1 antibody, which binds to the programmed death ligand 1 (PD-L1) receptor, thereby blocking its interaction with ligands PD-L1 and programmed death ligand 2 (PD-L2). The programmed cell death protein (PD-1) receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. PD-L1 and PD-L2 are expressed in antigen-presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.[2]

EAG comment: No comment.

2.3 Comparators

The comparators in the decision problem differ to those in the NICE scope (see Table 2.1).

EAG comment:

- The rationale for not using nivolumab plus ipilimumab as a comparator in the decision problem (for the sub-population with colorectal cancer) is not clearly explained, despite this comparator being requested in the NICE scope. The company have been asked to provide a clearer explanation. The company explained that [redacted] of patients with metastatic colorectal cancer (CRC) and confirmed MSI-H/dMMR would be offered pembrolizumab as *first-line* treatment (as per technology appraisal 709 (TA709)), and therefore second line pembrolizumab treatment (which is the line of therapy relevant to the current company submission (CS)) would only be considered for 10% of patients with metastatic CRC and confirmed MSI-H/dMMR. For this subset, the first-line therapy would usually be a chemotherapy agent, with nivolumab plus ipilimumab offered as the *first choice* second-line agent. This would seem to imply that nivolumab + ipilimumab is a comparator, i.e. the company's own description of the care pathway states that, at the position of pembrolizumab in this appraisal, which is second line following chemotherapy, nivolumab + ipilimumab would be used. Therefore, it does not seem correct when the company argue (see Table 2.1) that nivolumab + ipilimumab is ruled out because it is not appropriate following pembrolizumab fist line: *"Given that nivolumab with ipilimumab cannot be used to treat patients who received any prior treatment with an anti-PD-1 antibody, and pembrolizumab is the standard of care for patients with untreated metastatic colorectal cancer with MSI-H or dMMR, nivolumab with ipilimumab will be the treatment of choice*

for a small subset of people who receive fluoropyrimidine-based combination chemotherapy in first-line when the MSI-H/MMR status is not yet confirmed or where the progression of the disease requires fast acting chemotherapy." This 'small proportion' is the very population in the decision problem. Therefore, it would seem reasonable to regard nivolumab + ipilimumab as a valid comparator to second line pembrolizumab in CRC. This has been deemed a key issue.

- The rationale for not using single-agent irinotecan and raltitrexed as a comparator in the decision problem (for the sub-population with CRC), which was requested in the NICE scope, is based on clinical opinion that this agent is rarely prescribed in clinical practice. There is a need for the company to back up the rationale with more objective evidence, which it was asked to do in the clarification questions. The company responded by reiterating that *"single-agent irinotecan and raltitrexed are not considered relevant comparators in this appraisal as clinical expert opinion confirmed that they are not routinely used in clinical practice unless other treatments are contraindicated. This is well established and supported by opinion from TA716".* The EAG does not think this response provides a more objective rationale than previously provided, as again it is based on subjective opinion. The uncertainty about the validity of excluding this comparator is therefore a key issue.
- For the sub-population with endometrial cancer, the decision problem appears sufficiently similar to the NICE scope in terms of chemotherapy. The rationale for excluding hormone therapy appears to be valid.
- The NICE scope includes 'established management without pembrolizumab' as a valid comparator for all three sub-populations (colorectal tumours, endometrial tumours and gastric, biliary, or small intestine tumours). It might be reasonable to consider that ECM is a general term for any comparator, provided it is currently used in clinical practice in England and Wales. However, the NICE scope also specifies comparators in the same list, which leaves open the possibility that ECM might include comparators not listed in the NICE scope. Unfortunately, in the company's consideration of appropriate comparators, 'established management without pembrolizumab' has not been included explicitly in the decision problem, except under the gastric, small intestine and biliary cancer heading (see Table 2.1). Failure to include this term in the decision problem means that the company might not have considered all relevant comparators in their evidence (only the specified ones are to be covered). The company were asked to list all established clinical management options for each of the tumour sub-populations so the EAG can evaluate if all relevant comparators are included amongst those listed in the decision problem. The company responded by directing the EAG to the response to QB4a in the response to the request for clarification[3], but, again the term 'established clinical management without pembrolizumab' was only mentioned in relation to 'gastric, small intestine, and biliary cancer' If some established management options have not been included amongst the specified comparators in the decision problem this will lead to a biased evaluation of the evidence. Therefore, this is deemed a key issue.

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rate (RR)
- Duration of response (DOR)
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

These were all included in the decision problem.

EAG comment: No comment.

2.5 Other relevant factors

Subgrouping for tumour site and previous therapy was advised by the NICE scope if the evidence allowed. The decision problem states that cost effectiveness evidence for each tumour site has been carried out, but there is no information about subgrouping for previous therapy.

Pembrolizumab was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on 16 May 2022 for treatment of the following MSI-H or dMMR tumours in adults with:

- Unresectable or metastatic CRC after previous fluoropyrimidine-based combination therapy
- Advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation
- Unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Pembrolizumab received Food and Drug Administration (FDA) approval in 2019 for the treatment of MSI-H solid tumours in children and adults.

According to the company, no equality issues related to the use of pembrolizumab for treatment of MSI-H or dMMR solid tumours are foreseen (CS[2], Section B.1.4).

EAG comment:

- Subgrouping was carried out for tumour site where possible (only the KEYNOTE-158 trial had >1 tumour site). An overall analysis was not also carried out.
- Subgrouping for previous treatment was not carried out and there is no rationale given for this. This might be an important subgrouping analysis if previous treatment in the United Kingdom (UK) target population differs from that in the trials. The company have been asked to provide a rational approach in the clarification letter. The company responded by stating that *"no subgroup analysis by previous treatment was performed neither in the KEYNOTE-158 nor in the KEYNOTE-164 trials. Considering the small sample size within each tumour type and the inherent exploratory nature of subgroup analyses, no valid and reliable conclusions can be drawn about the effectiveness of the technology in subgroups".* The EAG would argue that until such subgroup analyses are performed it is unknown whether there will be sufficient statistical power. In addition, even if insufficient power exists, this does not prohibit a considered comparison of point estimates that might uncover potential threats to external validity that should be of interest to the committee. The company continued by stating that *"also, in KEYNOTE-158 the subgroup analysis by previous treatment across the four tumour types would potentially lead to misleading results as it would not take into account the heterogeneity across histologies".* The EAG notes that the appropriate approach would be to stratify each stratum of tumour type by previous treatment (rather than stratifying the entire cohort by treatment type) which would circumvent this problem. The company continues by saying, *"in KEYNOTE-164, two cohorts of patients (Cohort A and B) were enrolled based on previous lines of chemotherapy (at least two lines and one line of fluoropyrimidine-based combination therapies for cohort A and B, respectively). As shown in the response to A34, no substantial differences in prior treatments is seen within and between the two cohorts with 100% of participants being previously treated with fluoropyrimidine-based combination therapies."* The EAG would state in response that although there was homogeneity in previous fluoropyrimidine-based combination therapies, there was heterogeneity with respect to other treatments.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A systematic literature review (SLR) was conducted by the company to identify available evidence on the efficacy and safety of pembrolizumab and relevant comparators for each of the tumour sites of interest. The findings will be reported separately for each of the SLRs conducted.

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[2] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[4, 5] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the five SLRs undertaken to identify relevant clinical evidence for the efficacy and safety of pembrolizumab and the relevant comparators, across the five tumour sites of interest. The original searches were between August and November 2022 and in the case of searches for small intestine cancer, this was updated in February 2023 in response to the EAG's request for clarification.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Endometrial cancer	Small intestine cancer	Gastric cancer	Biliary cancer	Colorectal cancer
Electronic databases					
Embase (Ovid)	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2023/02/17 SD: 17/02/23	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2022/08/31 SD: 29/08/31
MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (Ovid)	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2023/02/16 SD: 17/02/23	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2022/08/26 SD: 29/08/22	DR: 2000-2022/08/31 SD: 29/08/31
CENTRAL (EBM Reviews Ovid)	DR:2000-2022/07 SD: 29/08/22	DR: 2000-2023/01 SD: 17/02/23	DR:2000-2022/07 SD: 29/08/22	DR:2000-2022/07 SD: 29/08/22	DR:2000-2022/07 SD: 29/08/22
Conferences searches via Northern Light Life Sciences Conference Abstracts					
ASCO 2019-2022	DR: 2019-2022/wk36 SD: 22/09/22	DR: 2019-2022/wk44 SD: 14/11/22	DR: 2019-2022/wk35 SD: 06/09/22	DR: 2019-2022/wk36 SD: 22/09/22	DR: 2019-2022/wk40 SD: 13/10/22
ESMO 2019-2022	DR: 2019-2022/wk36 SD: 22/09/22	DR: 2019-2022/wk44 SD: 14/11/22	DR: 2019-2022/wk35 SD: 06/09/22	DR: 2019-2022/wk36 SD: 22/09/22	DR: 2019-2022/wk40 SD: 13/10/22
Trials registries					
ClinicalTrials.gov	31/10/22	15/11/22	30/11/22	29/9/22	20/10/22

ASCO = American Society of Clinical Oncology; CS = company submission; DR = date range; ESMO = European Society for Medical Oncology; SD = search date

EAG comment:

General

- Searches were carried out across a good range of databases. Two relevant conference proceedings and the ClinicalTrials.gov registry were also searched. Where appropriate strategies utilised a recognised randomised controlled trial (RCT) study design filter from the Scottish Intercollegiate Guidelines Network (SIGN).
- The EAG noted a number of reporting errors which were rectified by the company at clarification. The EAG would draw attention to current best practice which recommends that the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item 8 of the PRISMA-S reporting checklist recommends.[6] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors".*[7]
- The company confirmed that separate searches specific to adverse events (AEs) were not conducted. Instead *"adverse events were considered relevant outcomes for study selection in the PICOS criteria, and the database searches did not restrict to clinical efficacy outcomes".*[3] Best practice suggests that it is unlikely that efficacy searches that include study design filters for RCTs will be sensitive enough to identify all safety data. Ideally, searches for AEs should be carried out alongside the efficacy searches.[8]
- The database searches for the clinical effectiveness SLR contained a limit for English language items only. Language limits should be used with caution as they risk missing potentially relevant records, however given the large numbers of records retrieved by the searches, the EAG considers this pragmatic approach acceptable. However, a more cautious approach may have been to exclude non-English papers at screening rather than at the searching stage. If translation was not possible at that point, the exclusion of the references could have been clearly documented in the PRISMA flowchart in a more transparent manner.

Small Intestine Cancer SLR

- The EAG noted that the structure for the small intestine cancer SLR, was much more complex than the approach taken by the other SLRs. The strategies also contained a number of issues, including missing synonyms for combined chemotherapy regimen (see Capeox, missing terms include XELOX, CAPOX, CAPE-OX or OxCap) and non-consequential redundant lines. The strategies for Embase, MEDLINE and CENTRAL also contained errors regarding line combinations in the interventions facet (see line #34 in the Embase strategy).[9] Of more concern, the strategies did not include terms for pembrolizumab. Given that a search combining a facet for small intestinal cancer and study design, similar to the searches for the other tumour sites, would have resulted in the smallest overall results set (n=902 without the interventions facet in the Embase search), the EAG asked to rerun these searches in line with the approach taken by the other SLRs: i.e., small intestine cancer + adapted Scottish Intercollegiate Guidelines Network (SIGN) RCT filter (Limits: 2000-date/English only) and screen the results to ensure that no relevant papers were missed by the original search. The company responded that *"due to the limited time available, it was not feasible to remove intervention terms entirely for this search. To capture all potentially relevant studies based on the comparators of interest, we have revised the search strategies with the following changes:*
    - *Added pembrolizumab*
    - *Updated CAPOX (added all synonyms)*
    - *Removed redundant oxaliplatin lines*

- *Added nab-paclitaxel*
- *Updated leucovorin synonyms (added folinic acid)".*[3]

- Whilst the EAG would have preferred to see the searches in the requested format, which would have been more transparent due to the complex nature of the line combinations in the interventions facet, all of the major errors appear to have been corrected in the updated searches and the EAG agrees that the searches are now fit for purpose. For further discussion regarding the additional single-arm trial on pembrolizumab in patients with previously treated advanced small bowel adenocarcinoma located by these searches please see Section 3.1.5.2.
- The EAG noted a disparity in the number of hits reported for the conference searches between the PRISMA flowchart (n=0) and the strategies listed in Section D1.2.2. (ASCO = 19, ESMO = 6), the company confirmed that the numbers reported in D1.2.2. were correct and provided an updated PRISMA flowchart.

Biliary Cancer SLR

- The EAG noted a disparity for the number of search results reported for the conference searching between the strategies listed in Section D1.4.1 (n=225) and the numbers listed in the PRISMA flowchart (n=370). The company confirmed that the numbers reported in the PRISMA flowchart were correct and provided both the strategies of two update searches and details of an additional 47 abstracts identified by additional searches that were not yet indexed in the Northern Light database at the time of searching.

Colorectal Cancer SLR

- The company confirmed that a reporting error had occurred in the PRISMA flowchart for the number of search results reported for the conference searching and provided an updated PRISMA flow diagram depicting the 1,506 conference abstract records recorded in the searches in Section D1.5.2.

3.1.2 Inclusion criteria

3.1.2.1 Endometrial cancer

An SLR was originally conducted to identify RCTs, single-arm and non-randomised trials evaluating the efficacy of interventions used for the treatment of advanced endometrial carcinoma patients with disease progression after prior therapy. This 'global SLR' had a broad scope, where any intervention recommended in treatment guidelines (e.g., National Comprehensive Cancer Network, (NCCN), European Society for Medical Oncology (ESMO)), in addition to those based on consultation with clinical experts in the UK, was of interest. However, only interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage (*'UK-specific SLR'*). The UK-specific eligibility criteria used in the search strategy for studies are presented in Table 3.2.

Table 3.2: Eligibility criteria used in search strategy for evidence in the endometrial cancer subgroup

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with advanced (metastatic and/or unresectable) endometrial carcinoma by histology Patients previously treated for advanced disease Female adults (≥18 years)	Performance status of 2 or higher (or equivalent) Stage I or II disease CNS metastasis Previously treated with anti-PD-1*/PD-L1 agents

Criteria	Inclusion criteria	Exclusion criteria
	ECOG performance status of 0-1 (or equivalent) Recurrent disease when stage not specified	
Interventions	Paclitaxel monotherapy Doxorubicin monotherapy Carboplatin monotherapy Carboplatin and paclitaxel Pembrolizumab	Radiation without chemotherapy Surgical intervention without systemic treatment Other non-pharmacologic treatments (e.g., hyperthermia)
Comparators	Unrestricted	–
Outcomes	At least one of the following outcomes: OS Progression-free survival (PFS) Time to progression (TTP) Duration of response (DOR) Objective response rate (ORR), disease control rate (DCR), and number of patients with complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) when available Any-cause and treatment-related adverse events (AEs) Any-cause and treatment-related grade 3-5 AEs Any-cause and treatment-related serious AEs (SAEs) Discontinuation due to AEs (DAEs) Patient-reported outcomes (e.g., EQ-5D, EORTC QLQ-C30)	–
Study design	Randomised controlled trials (RCTs) Non-randomised trials Single-arm trials	Case reports Case series Observational studies
Time	From 2000 onward	
Language	English language	

Based on Table 6 of CS appendices[9]

* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response

AE = adverse event; CNS = central nervous system; CR = complete response; CS = company submission; DAE = discontinuation due to adverse event; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire C30; EQ-5D = EuroQol 5D quality of life instrument; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PFS = progression-free survival; PR = partial response; SAE = serious adverse event; SD = stable disease; TTP = time to progression

EAG comment: It is important to note that the protocol above represents a revised protocol, only containing interventions deemed by the company to represent current UK practice, which is different to the inclusive original protocol. This post-hoc protocol change is a risk of bias.

3.1.2.2 Small intestine cancer

An SLR was conducted to identify RCTs, single-arm and non-randomised trials evaluating the efficacy of interventions used for the treatment of advanced small intestine cancer who progressed on prior

therapy. This 'global SLR' had a broader scope, where any intervention recommended in treatment guidelines (e.g., NCCN, ESMO), in addition to those based on consultation with clinical experts in the UK, was of interest.

Table 3.3: Eligibility criteria used in search strategy for evidence in the small intestine cancer subgroup

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with advanced (unresectable and/or metastatic) small intestine or small bowel adenocarcinoma Patients who were previously treated for advanced disease Adults (≥18 years) ECOG performance status 0 or 1 Recurrent disease when stage not specified Irrespective of MSI-H or dMMR status	ECOG performance status 2 or higher (or equivalent) Stage I or II disease Central nervous system metastasis Previously treated with anti-PD-1*/ PD-L1 agents
Interventions	FOLFOX ± bevacizumab CAPOX ± bevacizumab FOLFOXIRI ± bevacizumab 5-FU + leucovorin ± bevacizumab Capecitabine ± bevacizumab Paclitaxel (including nab-paclitaxel) Docetaxel	Radiation without chemotherapy Surgical intervention without systemic treatment Other non-pharmacologic treatments (e.g., hyperthermia)
Comparators	Unrestricted	–
Outcomes	At least one of the following outcomes: OS; PFS; TTP; DOR; ORR and number of patients with CR, PR, SD, or PD when available; drug-related AEs; grade 3-5 AEs (all, drug related); DAEs; SAEs; PROs (e.g., EQ-5D, EORTC QLQ-C30)	–
Study design	Randomised controlled trials Controlled clinical trials Non-randomised clinical trials, including single-arm interventional studies	Case reports Case series
Time	From 2000 onward	–
Language	English language	–

Based on Table 15 of CS appendices[9]

* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response

5-FU = fluorouracil; AE = adverse event; CAPOX = oxaliplatin plus capecitabine; CR = complete response; CS = company submission; DAE = discontinuation due to adverse event; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire C30; EQ-5D = EuroQol 5D quality of life instrument; FOLFOX = folinic acid, fluorouracil, oxaliplatin; FOLFOXIRI = folinic acid, fluorouracil, irinotecan, oxaliplatin; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; SAE = serious adverse event; SD = stable disease; TTP = time to progression

EAG comment:

- Pembrolizumab is not included as an intervention or comparator. The company was asked to explain how an SLR that does not include pembrolizumab will be of relevance to this submission. The

company stated that, *"the search strategy included search terms specific for interventions that were deemed representative of the standard therapies at the time of the regulatory evaluation and therefore search terms for pembrolizumab were not included. The search strategy has been revised to include pembrolizumab as search term and resulted in the identification of three additional studies. Please see response to A5 and A6 for details of the studies identified."*

- In the response to A5 the company stated that *"the new search identified an additional single-arm trial on pembrolizumab in patients with previously treated advanced small bowel adenocarcinoma (Pedersen, 2021).*[10] *Of the 40 patients treated with pembrolizumab in the trial, only four had MSI-H tumour. Patients in this study (regardless of MSI-H status) were older than in KEYNOTE-158 (median age 63 years [29–85] vs 58 [21 to 77]), and a greater number of patients had two prior lines of therapy (67.5% vs 22.2%), but they were similar for proportion of males and race. The study shows better PFS results for MSI-H patients compared to KEYNOTE-158 for the same tumour site whereas median OS was not reached in neither study. However, the results are likely be impacted by the small sample size, (only two PFS and OS events occurred), and should be interpreted with caution."*
- The EAG agrees that the very small number of patients with MSI-H status in Pedersen 2021 may diminish the value of its contribution to the clinical effectiveness evidence [10] The data provided by the company in Table 3.4 are not informative, and perusal of the primary source does not provide more information, other than that the number of progression and death events in this subgroup were 2/4 and 2/4 respectively. The results of Pedersen 2021[10] will therefore not be added to the clinical evidence section in this report.
- In the response to A6, the company state that the other 2 articles of relevance were Maio 2022[11] and Marabelle 2020[12], which provided data already available from KEYNOTE-158.
- Therefore, the new search conducted by the company does not appear to have picked up any significant new papers that should be added to the clinical efficacy evidence.

Table 3.4: PFS and OS results for KEYNOTE-158 and Pedersen 2021

	KEYNOTE-158 (small intestine cancer), n=27	**Pedersen 2021, n=4**
Median PFS (95% CI), months	23.4 (4.3, NR)	NE (2.5, NE)
Median OS (95% CI), months	Not reached (16.2, NR)	NE (2.5, NE)
Based on Table 1 in company response to clarification questions[3] CI = confidence interval NE = non-estimable; NR = not reached; OS = overall survival; PFS = progression-free survival		

3.1.2.3 Gastric cancer

An SLR was conducted to identify RCTs evaluating the efficacy of interventions used for the treatment of advanced gastric cancer patients who progressed on prior therapy. This represents a post-hoc change to the original SLR protocol, where non-randomised and single-arm studies were originally also included. This protocol change was for pragmatic reasons, relating to the large number of studies yielded by the search. This 'global SLR' had a broad scope, where any intervention recommended in treatment guidelines (e.g., NCCN, ESMO), in addition to those based on consultation with clinical experts in the UK, was of interest. However, only interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage ('UK-specific SLR').

Table 3.5: Eligibility criteria used in search strategy for evidence in the gastric cancer subgroup

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with advanced (unresectable and/or metastatic) gastric cancer by histology Patients previously treated for advanced disease Adults (≥18 years) ECOG performance status of 0-1 (or equivalent) Recurrent disease when stage not specified	Performance status of 2 or higher (or equivalent) Stage I or II disease Central nervous system metastasis Previously treated with anti-PD-1*/ PD-L1 agents
Interventions	Pembrolizumab 5-FU 5-FU plus methotrexate/leucovorin FOLFIRI/mFOLFIRI Irinotecan Irinotecan + cisplatin Paclitaxel Docetaxel Docetaxel + cisplatin Docetaxel + oxaliplatin	Other systemic therapies Radiation without chemotherapy Surgical intervention without systemic treatment Non-pharmacologic treatments (e.g., hyperthermia)
Comparators	Unrestricted	--
Outcomes	At least one of the following outcomes: OS, PFS, time to disease progression, objective response, CR, PR, SD, PD	--
Study design	Randomised controlled trials	Non-randomised controlled trials Single-arm trials Observational studies Case reports Case series
Time	From 2000 onward	
Language	English language	

Based on Table 26 of CS appendices[9]
* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response
5-FU = fluorouracil; CR = complete response; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = folinic acid, fluorouracil, irinotecan; mFOLFIRI = modified folinic acid, fluorouracil, irinotecan; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; SD = stable disease

EAG comment:

- The outcomes of quality of life and AEs are not included, although these outcomes are in the NICE scope and decision problem. The lack of these outcomes in the SLR means that otherwise relevant studies restricted to these outcomes would not be included. The company have been asked to add these outcomes to the review and include any additional relevant studies if required. The company

responded by stating that the table in the CS had been incorrect and that HRQoL and AEs had actually been included for this SLR. The EAG is satisfied with this response.

- Only RCTs are included, which was a pragmatic decision secondary to the large numbers of trials identified. This represents a post-hoc change to the protocol, as the original SLR was reported to include non-randomised and single-arm trials as well. This therefore creates a risk of bias.
- The restriction to RCTs is also at odds with the main clinical evidence submission, where non-randomised and single-arm trials are included. Given this, the company has been asked how it can be sure that all relevant non-randomised and single-arm trials related to gastric cancer are included in the main clinical evidence submission. The company responded by stating that *"while the use and selection of single-arm trials is justified in the context of rare malignancies such as some of the MSI-H cancers, a large amount of evidence was expected to be found in the unselected population with previously treated gastric cancer. Therefore, a pragmatic choice was made to limit the selection to RCTs which would have provided the most robust form of evidence that could be used as the source for comparator efficacy"*. The EAG notes that no RCTs for pembrolizumab versus the comparators were found, forcing the company to look at separate comparator data. Therefore, if potentially useful non-randomised evidence directly comparing pembrolizumab to the comparators were missed by the RCT-only approach, this would constitute a limitation.
- It is important to note that the protocol above represents a revised protocol, only containing interventions deemed by the company to represent current UK practice, which is different to the inclusive original protocol. This post-hoc protocol change is a risk of bias.

3.1.2.4 Biliary cancer

An SLR ('global SLR') was performed to identify RCTs, single-arm and non-randomised trials evaluating the efficacy of interventions recommended in treatment guidelines (e.g., NCCN, ESMO), in addition to those based on consultation with clinical experts in the UK, for the treatment of patients with advanced biliary cancer who have progressed on prior therapy. However, only interventions reflecting the current clinical practice in the UK have been identified and selected at full-text screening stage ('UK-specific SLR').

Table 3.6: Eligibility criteria used in search strategy for evidence in the biliary cancer subgroup

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with advanced (unresectable and /or metastatic) biliary adenocarcinoma (gall bladder of biliary tree – intrahepatic or extrahepatic cholangiocarcinoma) Previously treated for advanced disease Adults (≥18 years) ECOG performance status of 0-1 (or equivalent) Recurrent disease when stage not specified	Performance status of 2 or higher (or equivalent) Stage I or II disease CNS metastasis Previously treated with anti-PD-1*/PD-L1 agents Ampulla of Vater cancers
Interventions	Pembrolizumab 5-FU plus leucovorin mFOLFIRI* (irinotecan plus 5-FU plus leucovorin) mFOLFOX* (oxaliplatin plus 5-FU plus leucovorin) XELOX/CAPOX (oxaliplatin plus capecitabine) Oxaliplatin plus natrium folinate plus 5-FU	Radiation without chemotherapy Surgical intervention without systemic treatment Other non-pharmacologic treatments (e.g., hyperthermia)
Comparators	Unrestricted	–
Outcomes	At least one of the following outcomes: OS	

Criteria	Inclusion criteria	Exclusion criteria
	PFS Time to progression DOR ORR, disease control rate, and number of patients with CR, PR, SD, or PD when available Any-cause and treatment-related AEs Any-cause and treatment-related Grade 3-5 AEs Any-cause and treatment-related SAEs Discontinuation due to AEs Patient-reported outcomes (e.g., EQ-5D, EORTC QLQ-C30)	–
Study design	RCTs Non-randomised trials Single-arm trials	Case reports Case series Observational (prospective, retrospective) studies
Time	From 2000 onward	–
Language	English language	–

Based on Table 35 of CS appendices[9]

* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response

5-FU = fluorouracil; AE = adverse event; CAPOX = oxaliplatin plus capecitabine; CNS = central nervous system; CR = complete response; CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire C30; EQ-5D = EuroQol 5D quality of life instrument; mFOLFIRI = modified folinic acid, fluorouracil, irinotecan; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; ORR = objective response rate; OS= overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RCT =randomised controlled trial; SAEs = serious adverse events; SD = stable disease;

EAG comment: It is important to note that the protocol above represents a revised protocol, only containing interventions deemed by the company to represent current UK practice, which is different to the inclusive original protocol. This post-hoc protocol change is a risk of bias.

3.1.2.5 Colo-rectal cancer

An SLR was performed to identify RCTs, in addition to non-RCT for pembrolizumab, evaluating the efficacy of interventions used globally ('global SLR') for the treatment of patients with advanced CRC who have progressed on at least one prior line of therapy. However, only interventions reflecting the current clinical practice in the UK have been identified and selected at full-text screening stage ('UK-specific SLR').

Table 3.7: Eligibility criteria used in search strategy for evidence in the CRC subgroup

Category	Inclusion Criteria	Exclusion Criteria
Population	Patients with histologically proven locally advanced unresectable or metastatic (unresectable stage III or stage IV) CRC: Previously treated for advanced disease Adult (≥18 years) ECOG 0 or 1 Recurrent disease when stage not specified Irrespective of MSI-H or dMMR status	ECOG 2 or higher Populations with stage I or II disease Studies in patient with CNS metastasis Studies in patients previously treated with anti-PD-1* /PD-L1
Interventions	Globally used treatments: Second-line or beyond setting:	Radiation without chemotherapy

Category	Inclusion Criteria	Exclusion Criteria
	Fluorouracil plus leucovorin plus oxaliplatin (FOLFOX) in combination with bevacizumab, aflibercept, ramucirumab, cetuximab, or panitumumab Fluorouracil plus leucovorin plus irinotecan (FOLFIRI) in combination with bevacizumab, aflibercept, ramucirumab, cetuximab, or panitumumab Capecitabine plus oxaliplatin (CAPOX) in combination with bevacizumab Third-line or beyond setting: Regorafenib TAS-102 (trifluridine/tipiracil) Treatments relevant to clinical practice in the UK:* Second-line or beyond setting: Pembrolizumab Nivolumab plus ipilimumab FOLFOX/FOLFOX4/mFOLFOX6 FOLFIRI TAS-102 (trifluridine/tipiracil) Third-line or beyond setting: Regorafenib	Surgical intervention without systemic treatment Other non-pharmacologic treatments (e.g., hyperthermia) Treatments targeting liver metastases
Comparators	Unrestricted	–
Outcomes	At least one of the following outcomes: OS PFS TTP DOR ORR and number of patients with CR, PR, SD, and PD, when available. Drug-related AEs Grade 3-5 AEs (all, drug-related) Discontinuation due to AE SAEs Patient-reported outcomes (e.g., EQ-5D, EORTC QLQ-C30)	–
Study design	For non-pembrolizumab studies RCTs For studies on pembrolizumab: RCTs Non-randomised trials Single-arm trials	For non-pembrolizumab studies Non-RCTs, including single-arm trials Case series Case reports Observational (prospective, retrospective) studies For studies on pembrolizumab: Case series

Category	Inclusion Criteria	Exclusion Criteria
		Case reports Observational (prospective, retrospective) studies
Time	From 2000 onwards	–
Language	English language	–

Based on Table 15 of CS appendices[9]

* Anti-PD-1 are drugs that suppress the programmed cell death 1 protein, thereby upregulating the immune response

AE = adverse event; CNS = central nervous system; CR = complete response; CRC = colorectal cancer; CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of Life questionnaire C30; EQ-5D = EuroQol 5D quality of life instrument; FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RCT =randomised controlled trial; SAEs = serious adverse events; SD =stable disease; TAS-102 = tipiracil hydrochloride; TTP = time to progression; UK = United Kingdom

EAG comment:

- Nivolumab with ipilimumab is included as a comparator, whereas it is not included in the main clinical evidence submission. The EAG has been asked why it is appropriate to include it in the SLR but not in the main clinical evidence submission. The company responded by stating that, *"the inclusion of nivolumab with ipilimumab in the SLR eligibility criteria for the interventions/comparators was based on MSD original understanding of the treatments that pembrolizumab would displace if it was recommended. Further insights into the treatment pathway for colorectal cancer in the metastatic setting and patient eligibility to licensed treatments, allowed MSD to revise the list of relevant comparators of pembrolizumab in this appraisal, which is presented in the decision problem (Table 1 of document B of company submission), and excludes nivolumab with ipilimumab for the reasons described in the response to A18."* The EAG accepts this response as an explanation of the apparent contradiction. However, as explained in Section 2.3, please note that the EAG does not agree that nivolumab with ipilimumab should necessarily be excluded as a comparator.
- It is important to note that the protocol above represents a revised protocol, only containing interventions deemed by the company to represent current UK practice, which is different to the inclusive original protocol. This post-hoc protocol change is a risk of bias.

3.1.3 Critique of data extraction

The following applies to all the SLRs conducted across the different cancer types.

Two reviewers, working independently, reviewed all titles and abstracts and proceedings identified by the search according to the selection criteria, apart from outcome criteria, which were only applied during the screening of full-text publications. All studies identified as eligible studies during title and abstract screening were then screened at a full-text stage by the same two reviewers. The full-text studies identified at this stage were included for data extraction. Following reconciliation between the two investigators, a third reviewer was included to reach a consensus on any remaining discrepancies.

Two reviewers, working independently, extracted data from the final list of included studies. All data of interest (study, treatment and patient characteristics, and outcomes) were extracted from primary

publications, whereas only additional data reported for relevant outcomes of interest or subgroups of interest were extracted from subsequent publications. Any discrepancies between reviewers were resolved through discussion, involving a third reviewer if necessary. Data were stored and managed in a Microsoft Excel workbook.

EAG comment: No comment.

3.1.4 Quality assessment

The following applies to all the SLRs conducted across the different cancer types.

Two independent reviewers assessed study quality. Following reconciliation between the two investigators, a third investigator was included to reach a consensus for any remaining discrepancies. The Cochrane risk of bias tool version 2 was used to assess the risk of bias in RCTs.[13] This instrument is used to evaluate five key domains: 1) bias arising from the randomisation process, 2) bias due to deviations from intended interventions, 3) bias due to missing outcome data, 4) bias in the measurement of the outcome, and 5) bias in the selection of the reported result. The domains were assessed independently and in aggregate for an overall risk of bias judgment based on the following scale: low risk of bias, some concerns, or high risk of bias.

The Newcastle-Ottawa scale was used to assess the quality of single-arm and non-randomised studies.[14] This instrument was used to evaluate the quality of these studies based on 1) study group and selection, 2) comparability of the groups within studies (not applicable for single-arm studies), and 3) the ascertainment of either the exposure or outcomes of interest for case-control or cohort studies. Ranking of the study quality was done by using a 'star system' in which a study can be given a maximum of one star for each numbered item within the "Selection" and "Exposure" categories and a maximum of two stars for "Comparability" category.

EAG comment: No comment.

3.1.5 Evidence synthesis

3.1.5.1 Endometrial cancer

A total of 6,137 citations were identified from database searches of MEDLINE, Embase, and CENTRAL. After removing 1,145 duplicate citations, a total of 4,992 citations were screened. This led to the exclusion of 4,789 citations and resulted in the identification of 203 citations eligible for full-text screening. Of these, 141 were excluded, one for duplicate publication, 31 for study design, 77 for population, eight for intervention, 20 for outcome, four for other reasons (e.g., protocols, abstracts not identified from conference search, and full-text unavailable for review). This resulted in the inclusion of 62 citations from the main database searches. Searches of conference proceedings and the United States (US) trial registry, as well as handsearch of the bibliography of previously published SLRs resulted in the identification of 238 additional citations for screening, of which 29 were included. Overall, a total of 91 citations representing 61 unique trials met the eligibility criteria of the global SLR.

Of the 61 trials identified in the global SLR, 45 were excluded from the UK-specific SLR because they had evaluated interventions deemed 'not of interest' by the company. The remaining 16 trials (represented in 33 citations) consisted of three single-arm trials and 13 RCTs.

Of these 16 trials, four trials (three single-arm trials and one RCT) evaluating pembrolizumab were identified. Of these, KEYNOTE-146 and KEYNOTE-775 investigated the efficacy and safety of pembrolizumab in combination with lenvatinib and therefore are not in line with the intervention of interest in this appraisal (pembrolizumab monotherapy). Roque 2021 was reported to be a Phase 2

single-arm trial evaluating pembrolizumab in patients with recurrent MSI-H endometrial cancer analysed by whole exome sequencing (WES). Results from this trial are discussed in Document B, Section B.3.14.1.3 on the validation of the cost effectiveness analysis, but are not in the clinical effectiveness section. KEYNOTE-158 was the only study investigating the efficacy of pembrolizumab in the approved indication deemed relevant to this appraisal by the company.

Table 3.8: List of publications included in the UK-specific SLR

Trial ID	Registry number	Principal publication	Principal publication title	Associated publications
Angioli 2007	--	Angioli 2007	Liposome-encapsulated doxorubicin citrate in previously treated recurrent/metastatic gynecological malignancies	--
Hirai 2004	--	Hirai 2004	Phase II trial of 3-h infusion of paclitaxel in patients with adenocarcinoma of endometrium: Japanese Multicenter Study Group	--
Homesley 2008	--	Homesley 2008	A phase ii trial of weekly 1-hour paclitaxel as second-line therapy for endometrial and cervical cancer	--
KEYNOTE-146/Study 111	NCT02501096	Makker 2020	Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer	Makker 2019a; Makker 2019b; Makker 2020
KEYNOTE-158	NCT02628067	O'Malley 2019	Pembrolizumab in patients with msi-h advanced endometrial cancer from the keynote-158 study	Maio 2022, O'Malley 2022, O'Malley 2022
KEYNOTE-775	NCT03517449	Lorusso 2021	Health-related quality of life (HRQoL) in advanced endometrial cancer (aEC) patients (pts) treated with lenvatinib plus pembrolizumab or treatment of physician's choice (TPC).	Colombo 2021, Colombo 2021, Makker 2022, Makker 2022, Makker 2021, Makker 2022, Yonemori 2022
Lincoln 2003	--	Lincoln 2003	Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: A gynecologic oncology group study	--
McMeekin 2015	NCT00883116	McMeekin 2015	Phase iii randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer	CT.gov 2015
Muggia 2002	--	Muggia 2002	Phase ii trial of the pegylated liposomal doxorubicin in	--

Trial ID	Registry number	Principal publication	Principal publication title	Associated publications
			previously treated metastatic endometrial cancer: A gynecologic oncology group study	
Nishio 2003	--	Nishio 2003	Weekly 1-h paclitaxel infusion in patients with recurrent endometrial cancer: A preliminary study	--
Roque 2021	NCT02899793	Roque 2021	A phase II evaluation of pembrolizumab in recurrent microsatellite instability-high (MSI-H) endometrial cancer patients with Lynch-like versus MLH-1 methylated characteristics (NCT02899793)	Bellone 2021, Bellone 2022
Scambia 2020	NCT02725268	Scambia 2020	Randomized phase ii study of sapanisertib (sap) + paclitaxel (pac) versus pac alone in patients (pts) with advanced, recurrent, or persistent endometrial cancer	CT.gov 2020a
Vandenput 2009	--	Vandenput 2009	Leuven Dose-Dense Paclitaxel/Carboplatin Regimen in Patients With Primary Advanced or Recurrent Endometrial Carcinoma	--
Vandenput 2012	--	Vandenput 2012	Weekly paclitaxel-carboplatin regimen in patients with primary advanced or recurrent endometrial carcinoma	--
Van Wijk 2003	--	Van Wijk 2003	Phase ii study of carboplatin in patients with advanced or recurrent endometrial carcinoma. A trial of the eortc gynaecological cancer group	--
Vergote 2015	--	Vergote 2015	Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: A study in 108 patients by the Belgian Gynaecological Oncology Group	--

Based on Table 7 of the CS appendices[9]
aEC = advanced endometrial cancer; EORTC = European Organisation for the Research and Treatment of Cancer; G-CSF = Granulocyte colony-stimulating factor; HRQoL = health-related quality of life; MSI-H = microsatellite instability-high; SLR = systematic literature review; TPC = treatment of physician's choice; UK =United Kingdom

EAG comment:

- The CS claims that *"...except for paclitaxel in gastric cancer and paclitaxel/doxorubicin in endometrial, there were no published data available specifically in MSI-H/dMMR-specific populations"*. However, the EAG were able to find a trial of nivolumab with ipilimumab in this population. The company were asked to comment on the appropriateness of this trial to the decision

problem. The company were also asked to clarify if all studies were examined for subgroup data in the decision problem population. Finally, if some relevant clinical effectiveness data have been omitted from the CS, then the company were used to use this in the ITC comparisons. The company responded by stating that *"the study identified by the EAG was not used to perform an indirect treatment comparison as it evaluated an intervention MSD does not consider a relevant comparator in this appraisal for the reasons provided in the response to A18"*. The EAG does not agree with the arguments provided by the company in the clarification letter response[3] that nivolumab and ipilimumab is not an appropriate comparator, and therefore does not agree that the study in question should be included. This has been deemed a key issue.

- The specific reasons for the exclusion of 45 trials from the UK-specific SLR are not provided in Table 8 of the appendices. A general reason (*"interventions not of interest"*) is given in the text on page 14 of the appendices, but more detailed reasons for the exclusion of each study would be helpful to allow us to assess the validity of the exclusions. In the clarification questions, the company were asked if the company could provide specific reasons why each of the 45 trials is 'not of interest'. The company responded that *"the 45 citations excluded from the endometrial cancer UK-specific SLR …. were excluded because the interventions evaluated were not relevant to the UK clinical practice. As explained in the Appendix of the company submission, these 'global SLRs' had a broader scope and interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage ('UK-specific SLR'). This resulted in a number of studies being considered relevant to the 'global SLR' but excluded from the UK-specific SLR as eligibility criteria for the interventions were not met. Tables…. below provide details of the interventions evaluated in the excluded studies which were considered not relevant to current clinical practice in the UK"*. The tables provided listed the interventions deemed unsuitable for UK practice, and the EAG noted that none were the comparators used in the indirect treatment comparison (ITC). Given the company's definition of relevant comparators, these exclusions appear appropriate. However, given that the NICE scope allowed any established comparator, some of these exclusions may not be justified.

3.1.5.2 Small intestine cancer

Searching MEDLINE, Embase, and CENTRAL, 215 citations were identified. In the title and abstract screening phase, 39 duplicates were removed, 169 citations were excluded, and seven citations were moved forward into the full-text screening phase. In the full-text screening phase, four citations were excluded due to population, one due to intervention, and one due to study design. The only remaining study was single-arm trial (Overman 2018) that evaluated nab-paclitaxel that is not considered a relevant comparator.

EAG comment: There were no trials identified using pembrolizumab. This was due to pembrolizumab not being included as an intervention or comparator in the protocol. It is therefore unknown if relevant pembrolizumab trials relating to small intestine cancer exist in addition to KEYNOTE-158. This very serious issue has also been raised as an EAG comment in Section 3.1.2.2.

3.1.5.3 Gastric cancer

A total of 17,535 abstracts were identified across Embase, MEDLINE, and CENTRAL. After removing 4,375 duplicate records, 13,160 records were screened, resulting in the exclusion of 12,191 abstracts. The remaining 969 records were progressed to full-text screening, where 762 full-text publications were excluded for the following reasons: 73 due to study design, 625 due to population, 10 due to outcome, 49 due to intervention, and five due to other reasons (e.g., language, study protocol). A total of 207 full-text publications were included at this stage. An additional 825 citations were identified through

conference search (n=812), search of the US clinical trial registry (n=12), and handsearch of the grey literature (n=1); of these, 61 were included the evidence base. Overall, a total of 268 publications (representing 206 unique clinical trials) were of interest for the global SLR.

Of the 206 trials included in the global evidence base, 165 were excluded from the UK-specific SLR because they were not RCTs (n=142) or had evaluated interventions not of interest (n=23). The remaining 65 citations (representing 41 unique RCTs) were included in the evidence base.

Following clinical expert consultation, the final list of comparators reflecting current clinical practice in the UK were narrowed down by the company to paclitaxel and FOLFIRI (folinic acid, fluorouracil, irinotecan). Based on this, of the 41 trials that met the eligibility criteria for inclusion in the SLR, only 24 corresponding to 45 publications are considered relevant to this appraisal. A complete list of publications included after full-text review is available in Table 3.9. The studies not considered relevant for this appraisal by the company are shaded in the table.

Table 3.9: List of publications included in the UK SLR

Trial	Primary/ secondary	Author, year	Title
KEYNOTE-061	Primary	Shitara 2018	Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (keynote-061): A randomised, open-label, controlled, phase 3 trial
	Secondary	Shitara 2021	Molecular determinants of clinical outcomes with pembrolizumab versus paclitaxel in a randomized, open-label, phase 3 trial in patients with gastroesophageal adenocarcinoma
	Secondary	Fuchs 2020	Pembrolizumab versus paclitaxel for previously treated patients with pd-l1-positive advanced gastric or gastroesophageal junction cancer (gc): Update from the phase iii keynote-061 trial
	Secondary	Chao 2021	Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the keynote-059, keynote-061, and keynote-062 clinical trials
	Secondary	Van Cutsem 2021	Health-related quality of life in advanced gastric/gastroesophageal junction cancer with second-line pembrolizumab in KEYNOTE-061
	Secondary	Cutsem 2019	Impact of pembrolizumab (pembro) versus paclitaxel on health-related quality of life (hrqol) in patients with advanced gastric or gastroesophageal junction (gej) cancer that has progressed after first-line chemotherapy (keynote-061)
	Secondary	Fuchs 2022	Pembrolizumab versus paclitaxel for previously treated PD-L1-positive advanced gastric or gastroesophageal junction cancer: 2-year update of the randomized phase 3 KEYNOTE-061 trial
Yi 2012	Primary	Yi 2012	Randomised phase ii trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum
RAINBOW	Primary	Wilke 2014	Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (rainbow): A double-blind, randomised phase 3 trial
	Secondary	Al-Batran 2016	Quality-of-life and performance status results from the phase iii rainbow study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric or gastroesophageal junction adenocarcinoma
	Secondary	Cascinu 2021	Tumor response and symptom palliation from rainbow, a phase iii trial of ramucirumab plus paclitaxel in previously treated advanced gastric cancer
	Secondary	De Vita 2019	Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: Subgroup analysis from rainbow study
	Secondary	Kim 2018	Exposure-response relationship of ramucirumab in east asian patients from rainbow: A randomized clinical trial in second-line treatment of gastric cancer

Trial	Primary/ secondary	Author, year	Title
	Secondary	Muro 2016	Subgroup analysis of east asians in rainbow: A phase 3 trial of ramucirumab plus paclitaxel for advanced gastric cancer
	Secondary	Shitara 2016	Subgroup analyses of the safety and efficacy of ramucirumab in japanese and western patients in rainbow: A randomized clinical trial in second-line treatment of gastric cancer
	Secondary	Van Cutsem 2020	Biomarker analyses of second-line ramucirumab in patients with advanced gastric cancer from rainbow, a global, randomized, double-blind, phase 3 study
	Secondary	Yamaguchi 2021	Quality of life associated with ramucirumab treatment in patients with advanced gastric cancer in japan: Exploratory analysis from the phase iii rainbow trial
	Secondary	Muro 2019	Is ramucirumab and paclitaxel therapy beneficial for second-line treatment of metastatic gastric or junctional adenocarcinoma for patients with ascites? Analysis of rainbow phase 3 trial data
	Secondary	Muro 2018	Age does not influence efficacy of ramucirumab in advanced gastric cancer: Subgroup analyses of regard and rainbow
	Secondary	Klempner 2020	Impact of frontline doublet versus triplet therapy on clinical outcomes: Exploratory analysis from the rainbow study
SHINE	Primary	Van Cutsem 2017	A randomized, open-label study of the efficacy and safety of azd4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with fgfr2 polysomy or gene amplification
AIO	Primary	Thuss-Patience 2011	Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer - a randomised phase iii study of the arbeitsgemeinschaft internistische onkologie (aio)
JACCRO GC-05	Primary	Tanabe 2015	Phase ii/iii study of second-line chemotherapy comparing irinotecan-alone with s-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with s-1 (jaccro gc-05)
Sym 2013	Primary	Sym 2013	A randomized phase ii study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mfolfiri) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy
Shitara 2014	Primary	Shitara 2014	Randomised phase ii study comparing dose-escalated weekly paclitaxel vs standard-dose weekly paclitaxel for patients with previously treated advanced gastric cancer
ABSOLUTE	Primary	Shitara 2017	Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (absolute): An open-label, randomised, non-inferiority, phase 3 trial
	Secondary	Takashima 2019	Peritoneal metastasis as a predictive factor for nab-paclitaxel in patients with pretreated advanced gastric cancer: An exploratory analysis of the phase iii absolute trial

Trial	Primary/ secondary	Author, year	Title
Satoh 2015	Primary	Satoh 2015	Randomized phase ii trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer
TyTAN	Primary	Satoh 2014	Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of her2-amplified advanced gastric cancer in asian populations: Tytan - a randomized, phase iii study
Roy 2013	Primary	Roy 2013	A randomized phase ii study of pep02 (mm-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma
JCOG0407	Primary	Nishina 2016	Randomized phase ii study of second-line chemotherapy with the best available 5-fluorouracil regimen versus weekly administration of paclitaxel in far advanced gastric cancer with severe peritoneal metastases refractory to 5-fluorouracil-containing regimens (jcog0407)
TRICS/UMIN 000002571	Primary	Nishikawa 2015	Randomised phase iii trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric cancer refractory to s-1 monotherapy: Trics trial
CCOG0701	Primary	Nakanishi 2016	Phase ii multi-institutional prospective randomized trial comparing s-1 plus paclitaxel with paclitaxel alone as second-line chemotherapy in s-1 pretreated gastric cancer (ccog0701)
SUN-CASE	Primary	Moehler 2016	Sunitinib added to folfiri versus folfiri in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled phase ii aio trial with serum biomarker program
	Secondary	Nagel 2018	Cytokeratin-18 fragments predict treatment response and overall survival in gastric cancer in a randomized controlled trial
Maruta 2007	Primary	Maruta 2007	A clinical study of docetaxel with or without 5'dfur as a second-line chemotherapy for advanced gastric cancer
T-ACT Study	Primary	Makiyama 2020	Randomized, phase ii study of trastuzumab beyond progression in patients with her2-positive advanced gastric or gastroesophageal junction cancer: Wjog7112g (t-act study)
RADPAC	Primary	Lorenzen 2020	Phase iii randomized, double-blind study of paclitaxel with and without everolimus in patients with advanced gastric or esophagogastric junction carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (radpac)
Lee 2017	Primary	Lee 2017	A multicenter randomized phase ii study of docetaxel vs. Docetaxel plus cisplatin vs. Docetaxel plus s-1 as second-line chemotherapy in metastatic gastric cancer patients who had progressed after cisplatin plus either s-1 or capecitabine
KCSG ST10-01	Primary	Lee 2019	A phase iii study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer who failed in first-line therapy (kcsg st10-01)

Trial	Primary/ secondary	Author, year	Title
Kondo 2000	Primary	Kondo 2000 [15]	A phase iii randomized study comparing doxifluridine and 5-fluorouracil as supportive chemotherapy in advanced and recurrent gastric cancer
KNUH2008047	Primary	Kim 2015	Multi-center randomized phase ii study of weekly docetaxel versus weekly docetaxel-plus-oxaliplatin as a second-line chemotherapy for patients with advanced gastric cancer
DREAM	Primary	Kang 2018	Efficacy and safety findings from dream: A phase iii study of dhp107 (oral paclitaxel) versus IV Paclitaxel in patients with advanced gastric cancer after failure of first-line chemotherapy
WJOG 4007	Primary	Hironaka 2013	Randomized, open-label, phase iii study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: Wjog 4007 trial
TCOG GI-0801/BIRIP	Primary	Higuchi 2014	Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase iii trial (tcog gi-0801/birip trial)
Fushida 2016	Primary	Fushida 2016	Paclitaxel plus valproic acid versus paclitaxel alone as second-or third-line therapy for advanced gastric cancer: A randomized phase ii trial
COUGAR-02	Primary	Ford 2014	Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (cougar-02): An open-label, phase 3 randomised controlled trial
GOLD	Primary	Bang 2017	Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (gold): A double-blind, randomised, placebo-controlled, phase 3 trial
Bang 2015	Primary	Bang 2015	Randomized, double-blind phase ii trial with prospective classification by atm protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer
RAINBOW-Asia	Primary	Xu 2021	Efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW-Asia): a randomised, multicentre, double-blind, phase 3 trial
	Secondary	CT.gov 2017	A Study of Paclitaxel With or Without Ramucirumab (LY3009806) in Participants With Gastric or Gastroesophageal Cancer
NCT00991952	Primary	CT.gov 2009	Irinotecan Hydrochloride With or Without Alvocidib in Treating Patients With Advanced Stomach or Gastroesophageal Junction Cancer That Cannot Be Removed By Surgery
NCT01579578	Primary	CT.gov 2012	Assess the Efficacy of AZD8931 in Combination With Paclitaxel Versus Paclitaxel Alone in Patients With Gastric Cancer

Trial	Primary/ secondary	Author, year	Title
Xiaoying 2019	Primary	Xiaoying 2019	Comparison of efficacy and safety of second-line palliative chemotherapy with paclitaxel plus raltitrexed and paclitaxel alone in patients with metastatic gastric adenocarcinoma: A randomized phase ii trial
Wang 2021	Primary	Wang 2021	Apatinib plus paclitaxel versus placebo plus paclitaxel as second-line therapy in patients with gastric cancer with peritoneal carcinomatosis: A double-blind, randomized phase ii trial
KEYNOTE-063	Primary	Chung 2021	Pembrolizumab versus paclitaxel for previously treated advanced gastric or gastroesophageal junction cancer (KEYNOTE-063): A randomized, open-label, phase 3 trial in Asian patients
	Secondary	Cheol 2020	Pembrolizumab vs paclitaxel as second-line treatment for asian patients with pd-l1-positive advanced gastric or gastroesophageal cancer (gc) in the phase iii keynote-063 trial
BRIGHTER	Primary	Shah 2022	Randomized, Double-Blind, Placebo-Controlled Phase III Study of Paclitaxel +/- Napabucasin in Pretreated Advanced Gastric or Gastroesophageal Junction Adenocarcinoma
		NCT02178956, CT.gov 2014	A Study of BBI608 Plus Weekly Paclitaxel to Treat Gastric and Gastro-Esophageal Junction Cancer
OGSG0701	Primary	Kawase 2021	Randomized phase II study of Irinotecan-11 versus Paclitaxel versus each combination chemotherapy with S-1 for advanced gastric cancer that is refractory to S-1 or S-1 plus CDDP: OGSG0701
GATSBY	Primary	Thuss-Patience 2017	Trastuzumab emtansine versus taxane use for previously treated her2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (atsby): An international randomised, open-label, adaptive, phase 2/3 study
	Secondary	Shitara 2020	Efficacy of trastuzumab emtansine in Japanese patients with previously treated HER2-positive locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma: A subgroup analysis of the GATSBY study
	Secondary	Shah 2019	Biomarker analysis of the GATSBY study of trastuzumab emtansine versus a taxane in previously treated HER2-positive advanced gastric/gastroesophageal junction cancer
Kang 2012	Primary	Kang 2012	Salvage chemotherapy for pretreated gastric cancer: A randomized phase iii trial comparing chemotherapy plus best supportive care with best supportive care alone
Lu 2019	Primary	Lu 2019	Combination of apatinib mesylate and second-line chemotherapy for treating gastroesophageal junction adenocarcinoma

Based on Table 27 of the CS appendices[9]
CS = company submission; SLR =systematic literature review; UK = United Kingdom

EAG comment:

- The limitation of studies to those with the comparators paclitaxel and FOLFIRI is in line with the decision problem, but not in line with the NICE scope, which allowed any comparator established in UK practice for this population. As previously noted in Section 2.3, this narrowing of the scope may have led to some important evidence of clinical relevance being missed out.
- The specific *"not of interest"* reasons for the exclusion of 23 trials from the UK-specific SLR are not provided in Table 28 of the appendices. Detailed reasons for the exclusion of each study would be helpful to allow us to assess the validity of the exclusions. In the clarification questions, the company were asked if the company could provide specific reasons why each of the 23 trials is 'not of interest'. The company responded that *"the …. 23 citations excluded from the gastric cancer UK-specific SLR were excluded because the interventions evaluated were not relevant to the UK clinical practice. As explained in the Appendix of the company submission, these 'global SLRs' had a broader scope and interventions specifically reflecting the current clinical practice in the UK were identified and selected at full-text screening stage ('UK-specific SLR'). This resulted in a number of studies being considered relevant to the 'global SLR' but excluded from the UK-specific SLR as eligibility criteria for the interventions were not met. Tables….below provide details of the interventions evaluated in the excluded studies which were considered not relevant to current clinical practice in the UK"*. The tables provided listed the interventions deemed unsuitable for UK practice, and the EAG noted that none were the comparators used in the ITC. Given the company's definition of relevant comparators, these exclusions appear appropriate. However, given that the NICE scope allowed any established comparator, some of these exclusions may not be justified.
- None of the 41 'included' studies are in the clinical evidence section of the CS.[2] It is assumed that this is because none of these studies covered the population with H-MSI/dMMR, and/or they were used in the ITC. However, this is unclear. The company has been asked to explain this. The company responded by stating that *"in the gastric cancer SLR, 24 studies corresponding to 45 publications were considered relevant to this appraisal as evaluating interventions of interest in line with the decision problem. Of the 24 studies, three studies namely Chao et al. 2013 (KEYNOTE-061), Sym et al. 2013, and Moehler et al. 2016 (SUNCASE) (19) were selected and used in the ITC"*. The EAG is satisfied with this response.

3.1.5.4 Biliary cancer

A total of 5,183 citations were identified through database searches of MEDLINE, Embase, and CENTRAL. After removing 891 duplicate citations, a total of 4,292 citations were screened. This led to the exclusion of 3,924 citations and resulted in the identification of 368 citations eligible for full-text screening. Of these, 322 were excluded: four for duplicate publication, 17 for study design, 180 for population, 33 for intervention, 68 for outcome, and 20 for other reasons (e.g., protocols, abstracts not identified from conference search, and full-text unavailable for review). This resulted in the inclusion of 46 citations from the main database searches. Searches of conference proceedings and the US trial registry, as well as handsearch of the bibliography of previously published SLRs resulted in the identification of 791 additional citations for screening, of which 29 were included. Overall, a total of 75 citations representing 54 unique trials met the eligibility criteria of the global SLR.

Of the 54 trials identified in the global SLR, 46 did not evaluate the interventions relevant to the routine practice in the UK and were therefore excluded. The remaining nine trials (represented in 15 citations) were retained, which consisted of five single-arm trials and four RCTs. Two trials evaluating pembrolizumab were identified, of which KEYNOTE-028 is a Phase 1b study investigating a not approved dosage of pembrolizumab (10 mg/kg every two weeks). Therefore, the company decided that it is not in line with the intervention of interest in this appraisal. KEYNOTE-158 was the only study investigating the efficacy of pembrolizumab in the approved indication deemed by the company to be relevant to this appraisal.

Table 3.10: Trial and treatment characteristics of included studies

Trial ID	Registry number	Publications	Study design	Publication type	Treatment	N	Trial start date	Primary completion date	Region	Multicenter
Single-arm trials										
Hwang 2015	NCT01127555	Hwang 2015	Phase II, open-label	Full-text	mFOLFOX3 (oxaliplatin plus 5-fluorouracil plus leucovorin)	30	April, 2010	June, 2012	South Korea	Yes
KEYNOTE-028	NCT02054806	Piha-Paul 2020; Yung-Jue 2019	Phase Ib, open-label	Full-text	Pembrolizumab	24	February, 2014	April, 2021	International	Yes
KEYNOTE-158	NCT02628067	Piha-Paul 2020; Yung-Jue 2019; Marabelle 2020; Maio 2022	Phase II, open-label	Full-text	Pembrolizumab	104	December, 2015	June, 2026	International	Yes
Kim 2019b	NCT02350686	Kim 2019	Phase II, open-label	Full-text	XELOX (capecitabine plus oxaliplatin)	50	May, 2015	December, 2019	South Korea	Yes
Sinn 2013	NCT00356161	Sinn 2013	Phase II, open-label	Full-text	Oxaliplatin plus natrium folinate plus 5-fluorouracil	37	April, 2002	January 2010	Germany	No

Trial ID	Registry number	Publications	Study design	Publication type	Treatment	N	Trial start date	Primary completion date	Region	Multicenter
RCTs										
ABC-06	NCT01926236; EudraCT, 2013-001812-30	Lamarca 2021, Lamarca 2019, Lamarca 2022	Phase III, open-label	Full-text	Arm 1: ASC	162	February, 2014	January, 2018	United Kingdom	Yes
					Arm 2 : ASC plus mFOLFOX (oxaliplatin plus leucovorin plus 5-fluorouracil)					
Choi 2021	NCT03464968	Choi 2021, Won 2020	Phase II, open-label	Full-text	Arm 1: mFOLFOX (oxaliplatin plus leucovorin plus 5-fluorouracil)	118	July, 2015	February, 2020	Korea	Yes
					Arm 2: mFOLFIRI (irinotecan plus leucovorin plus 5-fluorouracil)					
NALIRICC	NCT03043547; EudraCT: 2016-003709-33	Vogel 2022	Phase II, open-label	Conference abstract	Arm 1: nal-Irinotecan plus 5- fluorouracil plus leucovorin	100	October, 2017	December, 2021	Germany	Yes
					Arm 2: 5-flurouracil plus leucovorin					

Trial ID	Registry number	Publications	Study design	Publication type	Treatment	N	Trial start date	Primary completion date	Region	Multicenter
NIFTY	NCT03524508	Yoo 2021, Changhoon 2021, Yoo 2022	Phase IIb, open-label	Conference abstract/poster	Arm 1: Liposomal irinotecan plus 5- fluorouracil plus leucovorin	174	September, 2018	September, 2020	Korea	Yes
					Arm 2: 5-fluorouracil plus leucovorin					

Based on Table 36 on the CS appendices [9]
ASC = active symptom control; CS = company submission

3.1.5.5 Colorectal cancer

The search retrieved a total of 39,745 records. After the removal of duplicates, the abstracts of 30,856 records were screened. Of the 1,424 records that proceeded to the full-text screening phase, 49 records describing 25 unique RCTs evaluating globally used treatments for patients with advanced CRC who had disease progression after at least one prior line of therapy were identified. Six records describing four unique non-RCTs evaluating pembrolizumab monotherapy were also identified. To identify RCTs evaluating treatments relevant to clinical practice in the UK, a decision rule was applied to include only those trials evaluating the following interventions: nivolumab plus ipilimumab, FOLFIRI, FOLFOX, FOLFOX4, mFOLFOX6, TAS-102, or regorafenib (third-line and beyond patients). After application of this decision rule, 36 records describing 15 unique trials and six records describing four unique non-RCTs evaluating pembrolizumab monotherapy were included in the SLR.

Following clinical expert consultation, the final list of comparators reflecting current clinical practice in the UK has been narrowed down to the following chemotherapy regimens: FOLFOX, FOLFIRI and TAS-102. Based on this, of the 15 RCTs trials that met the eligibility criteria for inclusion in the SLR, only 14 corresponding to 34 records are considered relevant to this appraisal.

Four trials evaluating pembrolizumab have been identified, of which Le 2015 and KEYNOTE-028 are Phase 2 and 1b studies, respectively, investigating a not approved dosage of pembrolizumab (10 mg/kg every two weeks) and therefore were not regarded by the company to be in line with the intervention of interest in this appraisal. Michalaki 2020 is an American Society of Clinical Oncology (ASCO) conference abstract with limited information about patient characteristics (e.g., previous lines of therapy), study methodology and outcomes. Whilst it met the eligibility criteria for the SLR, it was not possible to assess its relevance to this appraisal. KEYNOTE-164 was the only study investigating the efficacy of pembrolizumab in the approved indication deemed by the company to be relevant to this appraisal.

A complete list of publications included after full-text review is available in Table 3.11. The studies not considered relevant for this submission are shaded in the table.

Table 3.11: List of included trials in UK-specific SLR

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
Studies on pembrolizumab (single-arm trials)				
KEYNOTE-028	NCT02054806	O'Neil 2017	Safety and antitumor activity of the anti-pd-1 antibody pembrolizumab in patients with advanced colorectal cancer	--
KEYNOTE-164	NCT02460198	Le 2020	Phase ii open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: Keynote-164	Diaz 2020, Le 2021
Le 2015	NCT01876511	Le 2015	PD-1 Blockade in Tumors with Mismatch-Repair Deficiency	--
Michalaki 2020	--	Michalaki 2020	Safety and efficacy of pembrolizumab monotherapy in patients with advanced colorectal msi-h/dmmr cancers	--
Non-pembrolizumab studies (RCTs)				
BEYOND	EudraCT 2017-004519-38	Aparicio 2022	Randomized phase II trial of FOLFIRI-panitumumab compared with FOLFIRI alone in patients with RAS wild-type circulating tumor DNA metastatic colorectal cancer beyond progression to first-line FOLFOX-panitumumab: the BEYOND study (GEMCAD 17-01)	--
Cao 2015	--	Cao 2015	A multi-center randomized phase ii clinical study of bevacizumab plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for Chinese patients with metastatic colorectal cancer	--
CAPRI-GOIM	EudraCT 2009-014041-81	Ciardiello 2016	Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): A randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX	--
CONCUR	NCT01584830	Li 2015	Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer	Xu 2020

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
			(CONCUR): A randomised, double-blind, placebo-controlled, phase 3 trial	
ECOG 3200	--	Giantonio 2007	Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group study E3200	Reddy 2005
Li 2018	NCT01661270	Li 2018	Aflibercept plus FOLFIRI in Asian patients with pretreated metastatic colorectal cancer: A randomized phase iii study	--
Liu 2015	--	Liu 2015	A randomized phase ii clinical study of combining panitumumab and bevacizumab, plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for patients with metastatic colorectal cancer and KRAS mutation	--
Moore 2016	NCT01111604	Moore 2016	Randomized phase II study of modified FOLFOX6 in combination with ramucirumab or icrucumab as second-line therapy in patients with metastatic colorectal cancer after disease progression on first-line irinotecan-based therapy	--
Peeters 2010	NCT00339183	Peeters 2010	Randomized phase iii study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer	Bennet 2011, Peeters 2014, Peeters 2015
RAISE	NCT01183780	Tabernero 2015	Ramucirumab versus placebo in combination with secondline FOLFIRI in patients with metastatic colorectal cancer that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study	Cohn 2017, Lim 2019, Obermannova 2016, Tabernero 2018, Yoshino 2017, Yoshino 2019
RECOURSE	NCT01607957	Mayer 2015	Randomized trial of tas-102 for refractory metastatic colorectal cancer	Longo-Munoz 2017, Van Cutsem 2017, Van Cutsem 2018

Trial ID	Registry number	Principal publication	Principle publication title	Associated publication(s)
TERRA	NCT01955837	Xu 2018	Results of a randomized, double-blind, placebo-controlled, phase iii trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: The TERRA study	--
VELOUR	NCT00561470	Van Cutsem 2012[16]	Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen	Chau 2014, Joulain 2013, Ruff 2015, Ruff 2018, Tabernero 2014, Van Cutsem 2016, Van Cutsem 2020
Xie 2014	--	Xie 2014[17]	Safety and efficacy of second-line treatment with folinic acid, 5-fluorouracil and irinotecan (FOLFIRI) in combination of panitumumab and bevacizumab for patients with metastatic colorectal cancer	--
Yoshino 2012	JapicCTI-090880	Yoshino 2012[18]	TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial	--

Based on Table 45 of the CS appendices[9]

CS = company submission; dMMR = mismatch repair deficiency; DNA = deoxyribonucleic acid; KRAS = Kirsten rat sarcoma virus gene; MSI-H = microsatellite instability-high; PD-1 = Programmed cell death protein 1; RAS = rat sarcoma virus; RCT = randomised controlled trial; SLR = systematic literature review; UK = United Kingdom

EAG comment:

- The limitation of studies to those with the comparators FOLFOX, FOLFIRI and trifluridine-tipiracil (TAS-102) is in line with the decision problem, but not in line with the NICE scope, which allowed any comparator established in UK practice for this population, and also specified nivolumab. As previously noted in section 2.3, this narrowing of the scope may have led to some important evidence of clinical relevance being missed out.
- Roque 2021 (and associated papers Bellone 2021 and Bellone 2022) is highlighted as a relevant pembrolizumab trial in the endometrial cancer SLR. Although this was included in the cost effectiveness section of the CS[2], it was not presented in the clinical effectiveness section. The company have been asked to explain why this trial was not included as clinical effectiveness evidence in the CS[2] alongside KEYNOTE-158. The company responded by stating that *"Roque et al. 2021 refers to a conference abstract for the relevant study of patients with recurrent MSI-H endometrial cancers treated with pembrolizumab. Bellone et al. 2022 provides further data and KM functions for OS and PFS for the same study. This is a small investigator led study of 24 evaluable patients, compared with the 83 endometrial cancer patients observed in KEYNOTE-158. Patients in Bellone et al. 2022 were older (mean age 69 vs. 64.3) and the majority (50%) were FIGO stage 1 compared to KEYNOTE-158 where endometrial patients were disease stage IV or IVB (97.6%). Also, in Bellone et al. 2022 six patients (25%) harboured Lynch/Lynch- like tumours and 18 (75%) had sporadic endometrial cancer whereas details on the molecular pathways originating MSI-H/dMMR tumours are not available for KEYNOTE-158. Data from this study are therefore uncertain given the small patient population and may represent a healthier but older patient population not thought to be consistent with pivotal trials related to the licence. Comparison of Bellone et al. 2022 OS data with those from KEYNOTE-158 endometrial cancer patients shows outcomes are comparable although Bellone et al. 2022 has a shorter maximum follow up period. PFS data are similar between the two studies (but slightly improved for Bellone study) and any interpretation of tangible differences between the studies should be treated with caution given the small patient numbers. In summary:*

  Median PFS (Bellone study vs KEYNOTE-158): 25.8 months vs. 21.9 months

  Median OS (Bellone study vs KEYNOTE-158): 40 months vs. Not reached

  ORR (Bellone vs KN-158): 58% vs. 50.6%"

  The EAG does not agree with the company's reasons for not including the data from Bellone 2022 in the clinical effectiveness evidence. The data are probably underpowered, but the point estimates may still be informative, and therefore contribute to a fuller understanding of the clinical effects of pembrolizumab. Furthermore, although the patient population in Bellone is different to that in KEYNOTE-158, it falls within the scope of the decision problem. However, the EAG does not regard the exclusion of the study as a key issue, given that its inclusion would increase, rather than diminish, the positive pembrolizumab effects provided from KEYNOTE-158.
- KEYNOTE-028 and Le 2015 were excluded on the basis of dosage. However, the dosage of pembrolizumab is not specified in either the NICE scope nor the decision problem (nor, interestingly, in the protocol of the SLR). The company has been asked to clarify why these trials were omitted from the clinical evidence. With regard to KEYNOTE-028, the company responded by stating that, *"whilst neither the NICE scope nor the decision problem specify the dosage of pembrolizumab, the scope of this appraisal is to evaluate the clinical effectiveness and cost-effectiveness of pembrolizumab in the licensed indication. According to the Summary of Product Characteristics (SmPC) (20), the recommended dose of pembrolizumab in adults is either 200 mg every 3 weeks or*

400 mg every 6 weeks, as opposed to 10 mg/kg every 2 weeks administered in KEYNOTE-028. Therefore, efficacy evidence from this study is not relevant to this appraisal as it is not directly applicable to pembrolizumab at the dosage permitted in clinical practice. In addition, KEYNOTE-028 was conducted in the unselected population (i.e., regardless of MSI status) and only one patient each in the biliary cancer and colorectal cancer cohorts had MSI-H tumour. In light of this, the population of this study is not considered in line with the population of interest to this appraisal and KEYNOTE-158 and KEYNOTE-164 were the only studies identified in the biliary and colorectal SLR, respectively, investigating the efficacy of pembrolizumab in the approved indication relevant to this appraisal." With regard to Le 2015 the company made the same response in terms of the dose, adding that *"in addition, in this study only 11 patients (corresponding to cohort A) had mismatch repair–deficient (dMMR) colorectal cancer"*. In the light of these responses, particularly those highlighting the mismatch with dMMR status, the EAG agrees with the company's decision to exclude these studies.

- KEYNOTE-061 is an RCT that directly evaluates pembrolizumab versus paclitaxel in people with gastric solid tumours. A subgroup analysis is included for the relevant MSI-H/dMMR population. The EAG was therefore concerned why these data were not included as a key part of the clinical evidence. The company have been asked to include the comparative evidence of this trial and also use it to inform the economic model. The company responded that *"KEYNOTE-061 and the associated publication appendices contain a small MSI-H post-hoc subgroup analysis (15 pembrolizumab arm patients vs 51 in KEYNOTE-158). PFS and OS outcomes for this analysis group appear better than the results in KEYNOTE-158, based on comparisons of medians and the KM curves. The base-case model used standard independently fitted PSMs to model comparator efficacy sources (including the MSI-H subgroup in the base-case comparison with paclitaxel). In the table below, a comparison of the naïve ITC analysis presented in the CS comparing KEYNOTE-158 pembrolizumab gastric cancer patients with KEYNOTE-061 paclitaxel patients (Section B.2.9.1) is made with a within trial comparison of KN-061 and indicates that the current estimates informing the economic model are conservative. These estimates show that the small sample in KEYNOTE-061 performs better than the gastric cohort in KEYNOTE-158. This suggests that ICER estimates would be improved for this population if KEYNOTE-061 were included. An option has been included within the updated economic model to explore the likely impact on cost-effectiveness results. By setting the gastric paclitaxel option for both OS and PFS to "ITC HR" in the Model Controls sheet and selecting the "KN-061 within" (new option at the end of Model Controls sheet) this scenario can be inputted. Results should be interpreted with caution given that the proportional hazards assumption likely does not hold. Results are complicated given that both QALY weights applied in gastric, treatment waning and the impact of worse paclitaxel outcomes all interact and can have complex effects. However, in general results with this fixed-HR scenario improve cost-effectiveness results for pembrolizumab (i.e. compared with the base-case where PSMs are fit to the paclitaxel data from KEYNOTE-061)."* Table summarises the results in KEYNOTE-061. The EAG agrees that excluding the direct results from KEYNOTE-061 would appear to be conservative, given the more optimistic point estimates from the direct KEYNOTE-061 comparison compared to the indirect estimates. Alongside the issues cited by the company in using these results for a cost-effectiveness analysis, the company agrees that exclusion of this study is not a key issue.

Table 3.12: Relative effects of pembrolizumab versus paclitaxel in gastric cancer

Outcome	Pembrolizumab versus paclitaxel hazard ratio (95% CI)	
	KEYNOTE-158 pembrolizumab versus KEYNOTE-061 paclitaxel (as per naïve ITC in this CS)	KEYNOTE-061 pembrolizumab versus paclitaxel within trial comparison
OS	0.52 (0.25-1.09)	0.42 (0.13-1.31)
PFS	0.73 (0.36-1.51)	0.54 (0.19-1.54)

Based on Table 16 of the response to the request for clarification[3]
Comparison of unadjusted ITC estimates using KEYNOTE-158 versus a within trial analysis of KEYNOTE-061
CI = confidence interval; CS = company submission; ITC = indirect treatment comparison; OS = overall survival; PFS = progression-free survival

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Details of the included trials

3.2.1.1 KEYNOTE-158

KEYNOTE-158 was a one arm trial, evaluating the effects of pembrolizumab 200 mg once every three weeks (Q3W) on adults with advanced (unresectable and/or metastatic) endometrial, small intestine, gastric or biliary solid tumours who have progressed on standard of care therapy. Only cohort K, which restricts the population to people with solid tumours having MSI-H and/or dMMR status is relevant to this submission. Outcomes included objective response rate (ORR), duration of objective response (DOR), progression-free survival (PFS), overall survival (OS), adverse events (AEs) and HRQoL. Follow-up was 30 days for AEs and events of clinical interest (ECI) monitoring and 90 days for serious AE monitoring. However, follow-up duration was not given for OS, PFS, ORR, or HRQoL. The study was conducted in 54 centres in 18 countries, which did not include the UK. Table 3.13 summarises the trial.

Table 3.13: Details of KEYNOTE-158

Study	KEYNOTE-158 (NCT02628067)[11, 12, 19]
Study design	Phase II, open-label, non-randomised, multicentre study of pembrolizumab in previously treated participants who have locally advanced unresectable or metastatic rare cancers for whom prior standard first-line treatment had failed. The study is ongoing and includes Cohorts A to M that are either tumour biomarker unselected or based on tumour biomarker expression (biomarker enrichment). The results reported are from Cohort K. The criteria for Cohort K are defined as any advanced solid tumour, with the exception of colorectal cancer (CRC), which is microsatellite instability-high (MSI-H). MSI-H and/or dMMR status is verified by local polymerase chain reaction or immunohistochemistry (IHC) testing. Patients received pembrolizumab 200 mg every 3 weeks until progressive disease (PD), unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, administrative reasons, or the patient has received 35 trial treatments (approximately 2 years) with pembrolizumab.

Study	KEYNOTE-158 (NCT02628067)[11, 12, 19]
	After the end of treatment, each participant was followed for 30 days for AE and events of clinical interest (ECI) monitoring and 90 days for serious AE monitoring. Participants who discontinued treatment for reasons other than disease progression had posttreatment follow-up of disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants were followed by telephone contact for OS until death, withdrawal of consent, becoming lost to follow-up or the end of the trial, whichever occurs first.
Population	Adults with multiple types of advanced (unresectable and/or metastatic) solid tumours who have progressed on standard of care therapy. Evidence in this submission is related to the following mismatched repair (MMR) deficient or microsatellite instability-high (MSI-H) tumour sites in line with the GB Marketing Authorisation: • Endometrial cancer • Gastric cancer • Small intestine cancer • Biliary cancer (Cholangiocarcinoma)
Intervention(s)	Pembrolizumab 200 mg Q3W
Comparator(s)	None
Reported outcomes specified in the decision problem	Objective response rate (ORR) Duration of objective response (DOR) Progression-free survival (PFS) Overall survival (OS) Adverse events Health-related quality of life (HRQoL)
Eligibility criteria	
Key inclusion criteria	• ≥18 years of age on the day of signing informed consent. • A histologically or cytologically-documented, advanced (metastatic and/or unresectable) solid tumour that was incurable and for which prior standard first-line treatment had failed. • For participants in Cohort K, any advanced solid tumour (except CRC), which is MSI-H. • Radiologically measurable disease based on RECIST 1.1 confirmed by independent central radiologic review. • A performance status of 0 or 1 on the ECOG Performance Scale. • Life expectancy of at least 3 months. • Demonstrated adequate organ function.
Key exclusion criteria	• Had participated in any other pembrolizumab trial or received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or any other immune-modulating mAB. • A diagnosis of immune deficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. • An active autoimmune disease that had required systemic treatment in the past 2 years. • A prior anti-cancer mAB within 4 weeks prior to study Day 1 or had not recovered (i.e., ≤ Grade 1 or at baseline) from an AE due to mABs administered more than 4 weeks earlier. • Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or had not recovered (i.e., ≤ Grade 1 or at baseline) from an AE due to a previously administered agent.

Study	KEYNOTE-158 (NCT02628067)[11, 12, 19]
	• A known additional malignancy within 2 years prior to enrolment. • Known active CNS metastases and/or carcinomatous meningitis
Settings and locations	This study was conducted at 54 centres in 18 countries. No patients were recruited in the UK.
Trial drugs	Trial drug: pembrolizumab Dosage formulation: solution for infusion Dose strength: 25 mg/mL (100 mg/4 mL) Dose and regimen: 200 mg, Q3W, administered of Day 1 of each 21-day cycle Route of administration: IV infusion
Study Objectives	
Primary Objectives	To evaluate the ORR to pembrolizumab, based on RECIST 1.1 as assessed by independent central radiologic review, in biomarker selected participants with any one of multiple types of advanced (metastatic and/or unresectable) solid tumours (Cohorts A to K)
Secondary Objectives	• To determine the safety and tolerability of pembrolizumab • To evaluate DOR (based on RECIST 1.1 as assessed by independent central radiologic review) in participants receiving pembrolizumab • To evaluate PFS (based on RECIST 1.1 as assessed by independent central radiologic review) in participants receiving pembrolizumab • To evaluate OS in participants receiving pembrolizumab
Exploratory Objectives	• To compare ORR, DOR, and PFS based on irRECIST with these same measures derived using RECIST 1.1, both as assessed by independent central radiologic review • To describe the change in patient-reported outcome scores between baseline and postbaseline time points overall and according to the subgroup of best overall response using the EQ-5D and EORTC QLQ-C30 instruments.

Based on Tables 9 and 10 of the CS [2]
AE = adverse event; CNS = central nervous system; CRC = colorectal cancer; CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; DOR = duration of response; ECI = events of clinical interest; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = EuroQol 5D quality of life instrument; GB = Great Britain; HRQoL = health-related quality of life; IHC = immunohistochemistry; IV = intravenous; mAB = monoclonal antibody; MMR = DNA mismatch repair deficient; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; PFS = progression-free survival; Q3W = once every three weeks; RECIST = Response Evaluation Criteria in Solid Tumours

3.2.1.2 KEYNOTE-164

KEYNOTE-164 was a one arm trial, evaluating the effects of pembrolizumab 200 mg Q3W on adults with previously treated advanced (unresectable and/or metastatic) colorectal solid tumours. Outcomes included ORR, duration of response (DOR), PFS, OS, and AEs. Health-related quality of life was not included. Follow-up was 30 days for AEs and ECIs monitoring and 90 days for serious AE monitoring. However, follow up duration was not given for OS, PFS, ORR. The study was conducted in 34 centres in 10 countries, which did not include the UK. Table 3.14 summarises the trial.

Table 3.14: Details of KEYNOTE-164

Study	KEYNOTE-164 (NCT02460198)[20-22]
Study design	Phase II, open-label, non-randomised, multicentre study of pembrolizumab in patients with previously treated, unresectable, locally advanced or metastatic

Study	KEYNOTE-164 (NCT02460198)[20-22]
	microsatellite instability-high (MSI-H) and/or DNA mismatch repair deficient (dMMR) colorectal cancer (CRC). Recruitment for this study has completed. Eligible participants were recruited in Cohorts A and B. Cohort A (n=61): Participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who had been previously treated with at least 2 lines of standard of care therapies, which must have included fluoropyrimidine, oxaliplatin, and irinotecan. Cohort B (n=63): Participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who had been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan ± antivascular endothelial growth factor (anti-VEGF)/epidermal growth factor receptor (EGFR) monoclonal antibody (mAB). MSI-H and/or dMMR status was verified by local polymerase chain reaction or immunohistochemistry (IHC) testing. Patients received pembrolizumab 200 mg every 3 weeks until progressive disease (PD), unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, administrative reasons, or the patient has received 35 trial treatments (approximately 2 years) with pembrolizumab. After the end of treatment, each participant was followed for 30 days for AEs and events of clinical interest (ECI) monitoring and 90 days for serious AE monitoring. Participants who discontinued for reasons other than PD had post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants were followed for overall survival (OS) until death, withdrawal of consent, or the end of the study.
Population	Adults with previously-treated locally-advanced unresectable metastatic mismatched repair (MMR) deficient or MSI-H colorectal cancer
Intervention(s)	Pembrolizumab 200 mg, once every three weeks (Q3W)
Comparator(s)	None
Reported outcomes specified in the decision problem	Objective response rate (ORR) Duration of objective response (DOR) Progression-free survival (PFS) Overall survival (OS) Adverse events Health-related quality of life (HRQoL)
Eligibility criteria	
Key inclusion criteria	≥18 years of age on the day of signing informed consent. A histologically proven locally advanced unresectable or metastatic (Stage IV) CRC Locally confirmed dMMR or MSI-H CRC Previous treatment with standard of care therapies: at least 2 lines of fluoropyrimidine, oxaliplatin, and irinotecan (Cohort A) and at least 1 line of systemic fluoropyrimidine +oxaliplatin or fluoropyrimidine + irinotecan ± anti-VEGF/EGFR mAB (Cohort B) An ECOG performance status of 0 or 1 A life expectancy of greater than 3 months At least one measurable lesion by RECIST 1.1 as determined by central review for response assessment Demonstrated adequate organ function.

Study	KEYNOTE-164 (NCT02460198)[20-22]
Key exclusion criteria	An active autoimmune disease that had required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) A diagnosis of immunodeficiency or receipt of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment Known active CNS metastases and/or carcinomatous meningitis Prior mAB, chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or participant who had not recovered (i.e., ≤ Grade 1 or at baseline) from AEs due to a previously administered agent Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
Settings and locations	This study was conducted at 34 centres in 10 countries. No patients were recruited in the UK.
Trial drugs	Trial drug: pembrolizumab Dosage formulation: solution for infusion Dose strength: 25 mg/mL (100 mg/4 mL) Dose and regimen: 200 mg, Q3W, administered of Day 1 of each 21-day cycle Route of administration: IV infusion
Study Objectives	
Primary Objectives	Objective (Cohort A): To evaluate the ORR per RECIST 1.1 assessed by independent radiologist review of the 200 mg Q3W dose of pembrolizumab in participants with locally advanced unresectable or metastatic MMR deficient or MSI high CRC and who have been previously treated with standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan. Objective (Cohort B): To estimate the ORR per RECIST 1.1 assessed by central imaging vendor of the 200 mg Q3W dose of pembrolizumab in participants with locally advanced unresectable or metastatic MMR deficient or MSI high CRC and who have been previously treated with at least one line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody).
Secondary Objectives	In both Cohort A and Cohort B separately: To determine safety and tolerability of pembrolizumab. To evaluate duration of response (DOR), disease control rate (DCR) and progression-free survival (PFS) per RECIST 1.1 assessed by central imaging vendor and overall survival (OS).
Exploratory Objectives	For Cohorts A and B separately: To evaluate ORR, DOR, DCR and PFS per RECIST 1.1 assessed by investigator. To evaluate ORR, DOR, DCR and PFS per irRECIST 1.1 assessed by central imaging vendor. To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab.

Based on Table 9 and 10 of the CS[2]

AE =adverse events; CNS = central nervous system; CRC = colorectal cancer; CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; DOR = duration of response; DCR = disease control rate; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal Growth Factor Receptor HRQoL = health-related quality of life; IHC = immunohistochemistry; IV = intravenous; mAB = monoclonal antibody; MMR = DNA mismatch repair deficient; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; PFS = progression-free survival; Q3W = once every three weeks; RECIST = Response Evaluation Criteria in Solid Tumours; VEGF = vascular endothelial growth factor

EAG comment:

- KEYNOTE-164 does not include HRQoL as an outcome, despite this being in the NICE scope and the decision problem. The company was asked to provide an explanation for the lack of this key outcome. In addition, if quality of life data do exist for this trial, the company have been asked to provide them. The company responded by stating that, "*At the time of the study design, the KEYNOTE-164 trial was not a Merck-sponsored study and was funded by John Hopkins Center. As such, the trial was not originally designed as a registration study (i.e., to be used in Marketing Authorisation application) and did not aim to collect additional outcome data, such as health-related quality of life.*". The EAG considers that this is a rational explanation which precludes failure to present data that was collected.
- The population in KEYNOTE-158 appears slightly broader than the NICE scope and decision problem because the exact nature of previous standard treatment is not specified (in contrast to the NICE scope and decision problem, where the previous treatments, specific to each cancer type, are detailed). The company has been asked to provide the previous treatments given for each separate cancer type in KEYNOTE-158.The company responded that, "*The previous treatments, specific to each cancer type, detailed in the NICE scope are based on the Marketing Authorisation that was granted to pembrolizumab in the relevant indication as follows:*
  - *KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer after previous fluoropyrimidine-based combination therapy.*
  - *KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:*
    - *advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;*
    - *unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy*

  Table 17-Table 19 [Tables 3.15 to 3.17] *present the prior systemic treatments of participants in KEYNOTE-158 (Cohort K) and KEYNOTE-164 (Cohorts A and B) trials, respectively, for the tumour sites relevant to this appraisal. These show that prior treatments were in line with the NICE scope and Marketing Authorisation, with the vast majority (92.8%) of patients with endometrial cancer receiving platinum-based chemotherapy and 100% of patients with colorectal cancer in both Cohorts A and B receiving fluoropyrimidine-based combination therapy as prior line of chemotherapy regimen. Patients with biliary (cholangiocarcinoma), gastric and small intestine received chemotherapy regimens that are also considered representative of the standard of care in the UK*." The EAG is satisfied with this response.

Table 3.15: Participants with Prior Systemic Treatment – KEYNOTE-158 (Cohort K) (ASaT Population)

Prior Systemic Treatment	Tumour Type n (%)
Cholangiocarcinoma (N=22)	
Gemcitabine and cisplatin	14 (63.6)
Gemcitabine and oxaliplatin	5 (22.7)
Gemcitabine and capecitabine	0
Other chemo	1 (4.5)
Total prior systemic therapy	20 (91%)
Endometrial (N=83)	
Carboplatin cisplatin	75 (90.4)
Other chemo	2 (2.4)

Prior Systemic Treatment	Tumour Type n (%)
Total prior systemic therapy	6 (7.2) 83 (100%)
Gastric (N=51)	
Fluorouracil-containing regimen	28 (54.9)
Paclitaxel or carboplatin	9 (17.6)
Capecitabine and oxaliplatin	9 (17.6)
Other chemo	5 (9.8)
Total prior systemic therapy	51 (100%)
Small Intestine (N=27)	
Oxaliplatin and fluorouracil and leucovorin	16 (59.3)
Irinotecan and fluorouracil and leucovorin	1 (3.7)
Other chemo	8 (29.6)
Total prior systemic therapy	25 (93%)
Based on Table 17 of the response to request for clarification[3] ASaT = all subjects as treated	

Table 3.16: Participants with Specific Prior Oncologic Therapies - KEYNOTE-164 (Cohort A) (ASaT Population)

KEYNOTE-164	Pembrolizumab 200 mg n	(%)
Subjects in population	61	
With one or more systemic therapies	61	(100.0)
Chemotherapy	61	(100.0)
Biologics	53	(86.9)
Other	16	(26.2)
Summary of Prior Systemic Oncologic Therapies		
Chemotherapy	61	(100.0)
Fluoropyrimidine (S1, 5FU or capecitabine)	61	(100.0)
Prior oxaliplatin	58	(95.1)
Prior irinotecan	58	(95.1)
Detoxifying agent for antineoplastic	47	(77.0)
Biologics	53	(86.9)
Anti-EGFR	31	(50.8)
Cetuximab (or Erbitux)	25	(41.0)
Panitumumab (or Vectibix)	10	(16.4)
Anti-angiogenic	45	(73.8)
Bevacizumab (or Avastin)	45	(73.8)
Ziv-Aflibercept (or Zaltrap)	4	(6.6)
Other	16	(26.2)
Regorafenib (or Stivaga)	5	(8.2)
Trifluridine/tipiracil (or Lonsurf)	3	(4.9)
Other including experimental therapies	9	(14.8)
Based on Table 18 of the response to request for clarification[3] Every subject is counted a single time for each applicable row and column. 5-FU = 5-fluorouracil; ASaT = all subjects as treated; EGFR = Epidermal Growth Factor Receptor		

Table 3.17: Participants with Specific Prior Oncologic Therapies - KEYNOTE-164 (Cohort B) (ASaT Population)

KEYNOTE-164	Pembrolizumab 200 mg n	(%)
Subjects in population		
With one or more systemic therapies	63	(100.0)
Chemotherapy	63	(100.0)
Biologics	44	(69.8)
Other	11	(17.5)
Summary of Prior Systemic Oncologic Therapies		
Chemotherapy	**63**	**(100.0)**
Fluoropyrimidine (S1, 5FU or capecitabine)	63	(100.0)
Prior oxaliplatin	61	(96.8)
Prior irinotecan	41	(65.1)
detoxifying agent for antineoplastic	52	(82.5)
Biologics	**44**	**(69.8)**
Anti-EGFR	19	(30.2)
Cetuximab (or Erbitux)	7	(11.1)
Panitumumab (or Vectibix)	13	(20.6)
Anti-angiogenic	34	(54.0)
Bevacizumab (or Avastin)	34	(54.0)
Ziv-Aflibercept (or Zaltrap)	1	(1.6)
Other	**11**	**(17.5)**
Regorafenib (or Stivaga)	5	(7.9)
Trifluridine/tipiracil (or Lonsurf)	2	(3.2)
Other including experimental therapies	7	(11.1)

Based on Table 19 of the response to request for clarification[3]
Every subject is counted a single time for each applicable row and column.
5-FU = 5-fluorouracil; ASaT = all subjects as treated; EGFR = Epidermal Growth Factor Receptor

- Although the method of follow up for the outcome of OS is clearly outlined in the CS[2] (see Table 3.10 above), the timing and method of follow up for PFS, DOR and HRQoL is unclear for both KEYNOTE-158 and KEYNOTE-164. The company has been asked to provide information on the timing and method of follow up for all outcomes. The company responded fully and to the satisfaction of the EAG, as follows: "*Details on timing and method of follow-up for PFS, DOR and HRQoL are provided below for the KEYNOTE-158 and KEYNOTE-164 trials.*

  KEYNOTE-158

  In participants who discontinue study therapy without local site confirmed disease progression (PD), a radiologic evaluation is performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. Every effort is made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 ± 7 days) in the first year and every 24 weeks (168 ± 7days) after year 1 until (1) the start of new anticancer treatment, (2) disease progression per local site assessment, (3) death, or (4) the end of the trial, whichever occurs first. All tumour imaging (scheduled and unscheduled) should be submitted to the central imaging vendor for analysis. In addition, if the investigator obtains additional imaging, including other modalities, that are obtained at an unscheduled time point to determine if the participant has progressed as well as imaging obtained for other reasons but captures radiologic progression, all of these imaging scans should be sent to the central imaging vendor.Patient-reported outcomes (PROs) are assessed at every cycle for the first 4 cycles, then

every 3 cycles until 9 months, then every 4 cycles until PD while the participant is receiving study treatment, at the Treatment Discontinuation Visit, and at the 30-day Safety Follow-up Visit (the visit schedule should be Cycle 1, 2, 3, 4, 7, 10, 14, 18, 22, etc.). If the Treatment Discontinuation Visit occurs 30 days after the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, PROs do need to be repeated.

KEYNOTE-164

In participants who discontinue study therapy without confirmed PD by the site per irRECIST, tumour imaging is performed at the time of treatment discontinuation (± 4 weeks). In participants who discontinue trial treatment due to documented disease progression, this is the final required tumour imaging. If previous tumour imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumour imaging at treatment discontinuation is not required. In participants who discontinue trial treatment without documented disease progression, every effort is made to continue monitoring their disease status by radiologic imaging using the same imaging schedule of every 9 weeks (Q9W) for the first year, every 12 weeks (Q12W) thereafter to monitor disease status until the start of new anti-cancer treatment, disease progression, death, or the end of the study, whichever occurs first."

- No details are given of the 18 countries in KEYNOTE-158, and the 10 countries in KEYNOTE-164, where data were collected. The company have been asked to provide details and also provide the numbers from each country. The company responded as follows: "*The KEYNOTE-158 trial was conducted in the following 18 countries (number of patients is provided in brackets): Australia (n=[redacted]), Brazil (n=[redacted]), Canada (n=[redacted]), Colombia (n=[redacted]), Denmark (n=[redacted]), France (n=[redacted]), Germany (n=[redacted]), Israel (n=[redacted]), Italy (n=[redacted]), Japan (n=[redacted]), Mexico (n=[redacted]), Netherlands (n=[redacted]), Norway (n=[redacted]), Republic of Korea (n=[redacted]), Russian Federation (n=[redacted]), Spain (n=[redacted]), South Africa (n=[redacted]), and the United States (n=[redacted]). The KEYNOTE-164 trial was conducted in the following 10 countries: Australia (n=[redacted]), Belgium (n=[redacted]), Canada (n=[redacted]), France (n=[redacted]), Germany (n=[redacted]), Israel (n=[redacted]), Japan (n=[redacted]), Republic of Korea (n=[redacted]), Spain (n=[redacted]) and the United States (n=[redacted])".* The EAG notes that there are no UK patients, which may contribute the possibility that the external validity of the trials to the UK target population is sub-optimal (see Section 3.2.3.2).
- In both trials, people with an Eastern Cooperative Oncology Group (ECOG) of 2 or more were excluded, despite this exclusion not being specified by the NICE scope or the proposed decision problem. This effectively narrows the decision problem relative to the NICE scope. The company have been asked to provide a rationale for this decision, and to provide details of the number of patients excluded from analysis for this reason. The company responded by stating that, "*Clinical trials evaluating pembrolizumab, as well as other immunotherapies, commonly exclude patients with ECOG PS >1 due to poor level of fitness and comorbidities that make these patients less suitable for this type of treatment. Even though the licence does not specifically restrict pembrolizumab to patients with ECOG 0-1, the Blueteq system includes performance status as an eligibility criterion for patients to access pembrolizumab based on participant eligibility criteria from the supporting clinical trials, in addition to any other limitations imposed as part of the Marketing Authorisation. Therefore, even though NICE final scope does not explicitly restrict patient eligibility based on performance status, this eligibility criterion will be included in the Blueteq form if pembrolizumab is recommended for the indication subject to this appraisal. Also, this exclusion criterion in KEYNOTE-158 and KEYNOTE-164 is in line with current clinical practice in the UK in relation to the treatment with pembrolizumab*." The EAG is satisfied with this response.

3.2.2 Statistical analysis of the included studies

The statistical analyses in KEYNOTE-158 and KEYNOTE-164 is summarised in Tables 3.18 and 3.19.

3.2.2.1 KEYNOTE-158

Table 3.18: Statistical analysis of KEYNOTE-158

	KEYNOTE-158
Treatment Assignment	As it is a single treatment arm, participants were assigned to pembrolizumab by non-random assignment. The trial was open-label: the Sponsor, investigator and participant were aware of the treatment administered.
Efficacy Analysis Populations	All subjects as treated (ASaT) population for efficacy analysis defined as participants who received at least 1 dose of study intervention and the opportunity to have been followed for 6 months prior to data cut off. As of 15-OCT-2021, a total of 183 participants in Cohort K were included in the ASaT population for efficacy analysis for the following MSI-H tumour sites: endometrial (83 participants), gastric (51 participants), small intestine (27 participants), and biliary (22 participants).
Safety Analysis Populations	ASaT population defined as allocated subjects who have received at least one dose of study treatment.
Primary Endpoint	• ORR based on RECIST 1.1 as assessed by independent central radiologic review (IRC) – ORR is defined as the proportion of participants in the analysis population (ASaT) who have a confirmed complete response (CR) or partial response (PR).
Secondary Endpoint	• DOR, based on RECIST 1.1 as assessed by IRC. DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause (whichever occurs first). • PFS, based on RECIST 1.1 as assessed by IRC. PFS is defined as the time from allocation to the first documented disease progression or death due to any cause (whichever occurs first). • OS is defined as the time from allocation to death due to any cause. • Safety endpoints - Safety assessments included adverse events (AEs), serious AEs and Adverse event of special Interest (AEOSI)
Statistical Methods for Key Efficacy Analyses	• The point estimate and 95% confidence interval (CI) for the ORR, based on IRC using RECIST 1.1, were provided using an exact binomial distribution (Clopper and Pearson method). Participants without response data were counted as non-responders. • DOR and PFS, based on IRC review using RECIST 1.1, were summarised by Kaplan–Meier (KM) methods. • OS was summarised by KM methods. Participants were censored at last assessment if there was no PFS or OS event.
Statistical Methods for Key Safety Analyses	Safety was evaluated using descriptive statistics.
Interim and Final Analyses	The trial incorporates an adaptive design in which multiple interim analyses may be performed with the opportunity to modify the planned sample size.
Multiplicity	There is no planned multiplicity control for this trial. The study is an adaptive trial. The cumulative data are reviewed by the study team on an ongoing basis, with no multiplicity control.
Sample Size and Power	The study is still recruiting and may enrol up to approximately 350 participants with any of the tumour types eligible in Cohort K (MSI-H). As of 15-OCT-2021,

	KEYNOTE-158
	a total of 183 participants in Cohort K were allocated in the ASaT population for efficacy analysis for the following MSI-H tumour sites: endometrial (83 participants), gastric (51 participants), small intestine (27 participants), and biliary (22 participants).

Based on Table 13 of the CS[2]
AE = adverse event; AEOSI = adverse events of special interest; ASaT = all subjects as treated; CI = confidence interval; CR = complete response; CS = company submission; DCR = Duration of complete response; DOR = duration of response; IRC = independent central radiological review; KM = Kaplan Meier; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours

3.2.2.2 KEYNOTE-164

Table 3.19: Statistical analysis of KEYNOTE-164

	KEYNOTE-164
Treatment Assignment	As it is a single treatment arm, participants were assigned to pembrolizumab by non-random assignment. The trial was open-label: the Sponsor, investigator and participant were aware of the treatment administered.
Efficacy Analysis Populations	All subjects as treated (ASaT) population which included all allocated participants who received at least one dose of pembrolizumab. A total of 124 participants were included in the ASaT population (61 in Cohort A and 63 in Cohort B).
Safety Analysis Populations	ASaT population
Primary Endpoint	• ORR based on RECIST 1.1 as assessed by independent radiologist review (IRC). • ORR is defined as the proportion of the participants in the analysis population who have a complete response (CR) or partial response (PR).
Secondary Endpoint	• Safety and tolerability - The primary safety analysis was based on participants who experienced toxicities as defined by CTCAE, Version 4.0 criteria. • DCR, based on RECIST 1.1 assessed by central imaging vendor. DCR is defined as the percentage of participants who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks prior to any evidence of progression. • DOR, based on RECIST 1.1 assessed by central imaging vendor. For participants who demonstrate CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. • PFS, based on RECIST 1.1 assessed by central imaging vendor. PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. • OS is defined as the time from first day of study treatment to death due to any cause. Participants without documented death at the time of analysis were censored at the date of the last follow-up.
Statistical Methods for Key Efficacy Analyses	• In Cohort A, the point estimate, 95% confidence interval (CI), and p-value for testing the response rate is greater than 15% were provided using exact binomial method proposed by Clopper and Pearson. In Cohort B, the point estimate and 95% CI were provided using exact binomial method proposed by Clopper and Pearson. Participants in the primary analysis population (ASaT) without ORR data were counted as non-responders.

	KEYNOTE-164
	• For DCR, the point estimate, 95% confidence interval were provided using exact binomial method proposed by Clopper and Pearson. Participants in the analysis population (ASaT) with missing DCR are considered as disease not under control. • For DOR, Kaplan–Meier (KM) curves and median estimates from the KM curves were provided as appropriate. • For PFS and OS endpoints, KM curves and median estimates from the KM • curves were provided as appropriate.
Statistical Methods for Key Safety Analyses	Safety and tolerability were assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs for each cohort separately. Count and percentage of AE were provided.
Interim and Final Analyses	Interim Analysis • For Cohort A, an interim analysis was planned. • Timing: was performed when the first 40 participants were followed up for at least 18 weeks • There is no interim analysis planned for Cohort B. • Final Analysis • Timing: performed when all patients have been followed up for at least 6 months.
Multiplicity	Cohort A and Cohort B have been evaluated independently. No multiplicity adjustment in each cohort.
Sample Size and Power	The overall sample size is approximately 120. • Cohort A: The planned sample size was 60 participants. For the ORR per RECIST 1.1 assessed by independent radiologist review, the trial has 93% power to demonstrate that ORR of pembrolizumab is better than 15% at an overall one-sided 2.5% alpha level, if the underlying centrally reviewed RECIST 1.1 ORR of pembrolizumab is 35%. • Cohort B: The planned sample size was 60 participants.

Based on Table 13 of the CS[2]
AE = adverse events; ASaT = all subjects as treated; CI = confidence interval; CR = complete response; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; DCR = Duration of complete response; DOR = duration of response; IRC = independent central radiological review; KM = Kaplan Meier; MSI-H = microsatellite instability-high; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours

EAG comment: An 'all subjects as treated' approach was used in both trials, whereby a participant was only included in the analysis if at least one dose of the drug had been taken. This may limit the representativeness of the trial to the real-world, where some patients may not take a single dose, and may therefore over-estimate efficacy. The company were asked to comment on the rationale for this decision, and to provide details of the number of patients excluded from analysis for this reason. The company responded by stating that all patients enrolled had received at least one dose, and so all had been included. The EAG is therefore confident that the "all subjects as treated" approach will not have led to attrition bias.

3.2.3 Baseline characteristics

The baseline characteristics of KEYNOTE-158 and KEYNOTE-164 are summarised in Tables 3.20 and 3.21.

3.2.3.1 KEYNOTE-158

Table 3.20: Participant characteristics in KEYNOTE-158 (ASaT population only)

	Endometrial		Gastric		Small Intestine		Cholangiocarcinoma	
	n	%	n	%	n	%	n	%
Participants in population	83		51		27		22	
Sex								
Male	0	0	33	65%	17	63%	16	73%
Female	83	100%	18	35%	10	37%	6	27%
Age (Years)								
< 65	45	54%	22	43%	18	67%	13	59%
≥ 65	38	46%	29	57%	9	33%	9	41%
Mean	64.3		66.2		57.6		59.7	
SD	8.7		11.9		13.1		11.1	
Median	64		67		58		60.5	
Range	42 to 86		41 to 89		21 to 77		40 to 77	
Race								
American Indian or Alaska Native	1	1%	3	6%	2	7%		
Asian	5	6%	14	28%	3	11%	2	9%
Black or African American	3	4%	2	4%				
Multiple	2	2%	2	4%				
White, Asian	2	2%						
White	70	84%	32	63%	22	82%	20	91%
Missing	2	2%						
Ethnicity								
Hispanic or Latino	13	16%	6	12%	3	11%	2	9%
Not Hispanic or Latino	60	72%	40	78%	20	74%	18	82%
Not Reported	10	12%	4	8%	4	15%	2	9%
Unknown			1	2%				
Geographic Region								
US	16	19%	4	8%	7	26%	2	9%
Non-US	67	81%	47	92%	20	74%	20	91%
ECOG								
[0] Normal activity	38	46%	23	45%	15	56%	10	46%
[1] Symptoms, but ambulatory	45	54%	28	55%	12	44%	12	55%
Metastatic Staging								
M0	2	2%	0		1	4%	4	18%
M1	81	98%	51	100%	26	96%	18	82%
Overall Stage								
III							1	5%
IIIA					1	4%		
IIIB							1	5%
IIIC	2	2%						
IV	67	81%	47	92%	26	96%	14	64%
IVA							1	5%
IVB	14	17%	4	8%			5	23%

	Endometrial		Gastric		Small Intestine		Cholangiocarcinoma	
	n	%	n	%	n	%	n	%
Brain Metastases Present								
Yes			1	2%				
No	83	100%	50	98%	27	100%	22	100%
Number of Prior Lines of Therapy								
0					2	7%	2	9%
1	44	53%	28	55%	15	56%	11	50%
2	20	24%	11	22%	6	22%	6	27%
3	13	16%	9	18%	3	11%	1	5%
4	5	6%	2	4%	1	4%	2	9%
5 or more	1	1%	1	2%				
Sum of Target Lesions Measurable at Baseline (mm)								
Participants with data	83		51		27		22	
Mean	91.9		78.9		63		89.9	
SD	70.8		60.4		38.9		61.3	
Median	71.1		62.9		55.3		80.8	
Range	11.8 to 282.8		14.4 to 255.9		14.8 to 165.5		21.3 to 231.1	
Prior Radiation Therapy								
Yes	54	65%	14	28%	2	7%	3	14%
No	29	35%	37	73%	25	93%	19	86%
PD-L1 Status								
Positive	10	12%	6	12%	2	7%	3	14%
Negative	2	2%	5	10%	5	19%	2	9%
Not Evaluable	1	1%						
Missing	70	84%	40	78%	20	74%	17	77%

Based on Table 12 of the CS[2]

ASaT = all subjects as treated; CS = company submission; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed death-ligand 1; SD = standard deviation; US = United States

3.2.3.2 KEYNOTE-164

Table 3.21: Participant characteristics in KEYNOTE-164 (ASaT population only)

	Total	
	n	(%)
Participants in population	124	
Sex		
Male	69	(55.6)
Female	55	(44.4)
Age (Years)		
≤65	83	(66.9)
>65	41	(33.1)
Mean	56.1	
SD	14.9	
Median	55.5	
Range	21 to 84	
Race		
Asian	33	(26.6)
Black or African American	7	(5.6)
White	84	(67.7)

	Total	
	n	(%)
Ethnicity		
Hispanic or Latino	4	(3.2)
Not Hispanic or Latino	119	(96.0)
Not reported	1	(0.8)
ECOG PS		
0	51	(41.1)
1	73	(58.9)
Cancer Stage		
IV	124	(100.0)
Metastatic Staging		
M0	4	(3.2)
M1	120	(96.8)
History of Brain Metastases		
No	124	(100.0)
MSI-High Status[a]		
POSITIVE	123	(99.2)
NEGATIVE	1	(0.8)
KRAS Status		
MUTANT	39	(31.5)
WILD TYPE	74	(59.7)
NRAS Status		
MUTATION DETECTED	7	(5.6)
MUTATION NOT DETECTED	56	(45.2)
UNDETERMINED	61	(49.2)
Mutation Status (Tougeron)[b]		
MUTANT	15	(12.1)
WILD TYPE	61	(49.2)
UNDETERMINED	48	(38.7)
BRAF Status		
MUTANT	15	(12.1)
WILD TYPE	61	(49.2)
UNDETERMINED	48	(38.7)
Prior Adjuvant/Neo-Adjuvant Therapy		
Yes	38	(30.6)
No	86	(69.4)
Baseline Tumour Size (mm) Based on IRC Assessment per RECIST 1.1		
Participants with data	124	
Mean	98.2	
SD	78.9	
Median	77.0	
Range	10.4 to 407.6	

Based on Table 11 of the CS[2]

Number of participants: all-participants-as-treated population, Cohort A and Cohort B

Cohort A: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least two lines of standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan

Cohort B: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least one line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody)

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

	Total	
	n	(%)

[b] A participant with a KRAS or NRAS status of Mutant is classified as Mutant. A participant with a KRAS status of Wild Type and NRAS status of Mutation Not Detected is classified as Wild Type, else the participant is classified as Undetermined

Database cut-off date: 19FEB2021

ASaT = all subjects as treated; BRAF = BRAF is a gene that encodes the B-Raf protein; ;CRC = colorectal cancer; CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EGFR = epidermal growth factor receptor; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; IRC = independent radiologist review committee; KRAS = Kirsten rat sarcoma virus gene; MSI = microsatellite instability; MSI-H = microsatellite instability-high; NRAS = enzyme encoded by the NRAS gene; PCR = polymerase chain reaction; RECIST = Response Evaluation Criteria in Solid Tumours; SD = standard deviation; US = United States; VEGF = vascular endothelial growth factor

EAG comment: To evaluate the external validity of the trial results, it is important to be aware of the characteristics of the UK target population, and to assess how closely these approximate to the characteristics of the trial populations. The company have therefore been asked to provide, where known, the characteristics of the UK target population (stratified by endometrial, colorectal, gastric, biliary and small intestine) in terms of age, race, cancer stage, metastasis stage, number of prior lines of therapy, prior radiation therapy, and PD-L1 status. The company responded as follows: *"Limited information on MSI-H patients is available. However, clinical experts when consulted at the advisory board raised no concerns in relation to the representativeness of the trial population to the UK target population. The following information is based on relevant tumour types regardless of MSI status and stage of cancer. Though these cancers can occur in adults of any age, the rates of diagnosis generally increase with age and rise steeply from age 50. In the UK in 2016-2018, on average each year half of new cases (50%) were in people aged ≥75 and ≥70 for gastric and small intestine cancers, respectively, whereas about 60% of new cases were in people aged ≥70 and ≥65 for colorectal and endometrial cancers, respectively (23-26); more than half of new cases (53%) of gallbladder cancer were in people aged 75 and over (27). As presented in the company submission, there is evidence to suggest Lynch syndrome-associated colorectal carcer has an earlier age of onset, with a crude median age at diagnosis of 52 years versus 69 years in sporadic disease. This may also be associated with earlier detection of Lynch syndrome due to cascade genetic testing in families where other members have already been diagnosed with Lynch-syndrome-associated cancers. With the exception of endometrial cancer, the majority of the population diagnosed are male. Incidence rates are lower in non-white minority ethnic groups compared with the white group in all relevant tumour sites ([see table below])."*

Table 3.22: Incidence statistics by age, sex and ethnic group for each tumour site, all MSI status

	Peak rate of diagnosis in the UK	Proportion of females diagnosed in England	Number (%) of cases by broad ethnic group in England, 2013–2017 (annual average)
Colorectal cancer	85–89	44%	White (90%) Asian (2.1%) Black (1.4%) Mixed/multiple (0.3%)
Endometrial cancer	75–79	100%	White (86%) Asian (4.1%) Black (2.2%) Mixed/multiple (0.5%)
Gastric cancer	85–89	35%	White (88%) Asian (3.0%)

	Peak rate of diagnosis in the UK	Proportion of females diagnosed in England	Number (%) of cases by broad ethnic group in England, 2013–2017 (annual average)
			Black (2.7%) Mixed/multiple (0.5%)
Small intestine cancer	80–84	45%	White (89%) Asian (3.1%) Black (2.1%) Mixed/multiple (<20 cases)
Biliary cancer	(gallbladder cancer) 85–89	(gallbladder cancer) 71%	(gallbladder cancer) White (84%) Asian (6.1%) Black (2.8%) Mixed/multiple (<20 cases)
Based on Table 21 of the response to the request for clarification[3], which was sourced from: Cancer Research UK[23, 24] for age and sex data, Delon 2022[25] for ethnicity MSI = microsatellite instability; UK = United Kingdom			

The characteristics of participants in the trials appeared similar to those in the UK data above for endometrial and biliary cancer. For colorectal and gastric cancer, and to a lesser extent small intestine cancer, the EAG notes large differences in ethnicity between the trials and the UK data above, although gender data appeared well-matched. The EAG recognises that microsatellite instability (MSI) status is not restricted to MSI-H in the UK data provided by the company, and so it is possible that the ethnic proportions in a UK subgroup of people with colorectal, gastric and small intestine cancer restricted to MSI-H status might be different to the ethnic proportions in the UK data provided by the company. This implies, with a large amount of uncertainty, that the ethnic make-up of the restricted target population might be more closely aligned with the trial data than was observed for the non-restricted UK data. Such a difference in ethnicity between a non-restricted and restricted (MSI-H) population would be more likely to occur if MSI-H status varied with ethnicity. However, given evidence that MSI status is not strongly linked to ethnicity (Ashktorab 2016),[26] it is unlikely that the ethnic make-up of a UK MSI-H subgroup would be appreciably different to the non-restricted UK data provided by the company. Therefore, given the difference in ethnicity between the trials and the unrestricted UK population, it appears probable that there would also be a difference in ethnicity between the trials and the restricted UK target population. This may lead to a reduction of external validity of trial results if ethnicity is an effect modifier. No subgrouping for ethnicity was carried out by the company, and so the external validity of trial results remains unknown. This has been flagged as a key issue.

3.2.4 Risk of bias assessment

3.2.4.1 KEYNOTE-158

KEYNOTE-158 study quality scored 6 on the Newcastle-Ottawa Scale, due to being single-arm trial which resulted in some domains being not applicable (i.e., selection of the non-exposed cohort and comparability of cohorts). The company stated that it was indicative of low risk of bias across all relevant domains.

Table 3.23: Newcastle-Ottawa quality assessment for KEYNOTE-158

Trial ID	Selection				Comparability	Outcomes			Final score
	1	2	3	4	1	1	2	3	
KEYNOTE-158	1	NA	1	1	NA	1	1	1	6
Based on Table 54 of the CS appendices[9]									

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for comparability
Selection
1) Representativeness of the exposed cohort
2) Selection of the non-exposed cohort
3) Ascertainment of exposure
4) Demonstration that outcome of interest was not present at start of study
Comparability
1) Comparability of cohorts on the basis of the design or analysis
Outcome
1) Assessment of outcome
2) Was follow-up long enough for outcomes to occur
3) Adequacy of follow up of cohorts
CS = company submission; NA = not applicable

3.2.4.2 KEYNOTE-164

KEYNOTE-164 study quality scored 6 on the Newcastle-Ottawa scale, due to being single-arm trial which resulted in some domains being not applicable (i.e., selection of the non-exposed cohort and comparability of cohorts). The company stated that it was indicative of low risk of bias across all relevant domains.

Table 3.24: Newcastle-Ottawa quality assessment for KEYNOTE-164

Trial ID	Selection				Comparability	Outcomes			Final score
	1	2	3	4	1	1	2	3	
KEYNOTE-164	1	NA	1	1	NA	1	1	1	6

Based on Table 55 of the CS appendices[9]
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for comparability
Selection
1) Representativeness of the exposed cohort
2) Selection of the non-exposed cohort
3) Ascertainment of exposure
4) Demonstration that outcome of interest was not present at start of study
Comparability
1) Comparability of cohorts on the basis of the design or analysis
Outcome
1) Assessment of outcome
2) Was follow-up long enough for outcomes to occur
3) Adequacy of follow up of cohorts
CS = company submission; NA = not applicable

EAG comment: The quality assessment of the trials using the Newcastle-Ottawa scale yielded a 'low risk of bias' (see Section B.2.5 in CS[2]). The measured effect in single-arm trials is not equal to treatment efficacy because without a control group it is impossible to determine the extent to which intervening variables such as placebo effect or natural recovery may have also contributed to the measured effect. In the absence of such information, it is quite possible that any measured benefit is wholly due to the intervening variables, and that the treatment therefore has no beneficial effect. It is even possible that the treatment may exert an actual harm, but any net benefit is due to the intervening variables. Therefore, the internal validity of single-arm trials is maximally compromised, and they will always be at very high risk of bias. Given this, the company have been asked to explain how single-arm trials can be at low risk of bias. The company have responded by reiterating that according to the scale the trials would be 'high quality'. The EAG would interpret this as a relative term, and maintain that the inevitable selection bias present in one arm trials renders a critical risk of overall bias.

3.2.5 Efficacy results of the included studies

3.2.5.1 Overall survival

3.2.5.1.1 KEYNOTE-158

Treatment with pembrolizumab suggested a prolonged benefit with respect to OS. Median OS was not reached in two tumour sites (endometrial and small intestine), and at 24 months OS rates were greater than or equal to 50% in each tumour site (Table 3.25).

Table 3.25: Summary of overall survival by tumour site (ASaT population for efficacy analysis)

KEYNOTE-158	Endometrial (N=83)	Gastric (N=51)	Cholangio-carcinoma (N=22)	Small intestine (N=27)
Death (%)	32 (38.6)	29 (56.9)	16 (72.7)	10 (37.0)
Median survival (months)[a]	Not reached	26.9	19.4	Not reached
95% CI for median survival[a]	(48.0,NR)	(6.6,NR)	(6.5,44.8)	(16.2,NR)
OS rate at 6 months in % [a]	85.5	66.7	81.8	92.6
OS rate at 12 months in % [a]	73.3	54.8	63.6	77.8
OS rate at 18 months in % [a]	70.6	52.8	50.0	70.4
OS rate at 24 months in % [a]	67.2	50.0	50.0	62.7

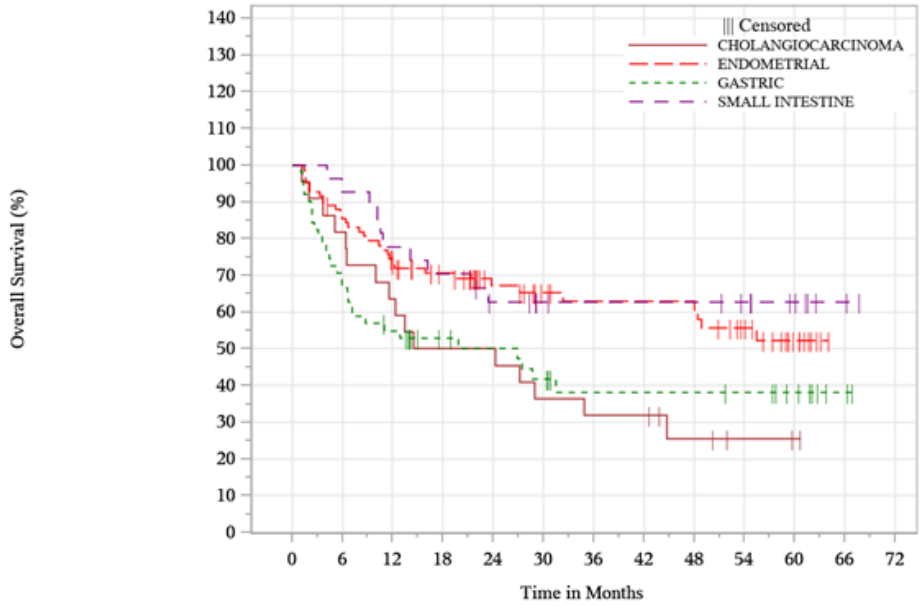
Based on Table 25 of the CS[2]

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

Participants who received at least one dose of pembrolizumab in KEYNOTE-158 with MSI-H tumours in cohort K with 6 months follow-up are included.

ASaT = all subjects as treated; CS = company submission; MSI-H = microsatellite instability-high; NR = not reached; OS = overall survival

Figure 3.1 KM estimates of overall survival by tumour site (ASaT population for efficacy analysis)



Based on Figure 10 of the CS[2] (Database cut-off date: 15OCT2021)

ASaT = all subjects as treated; CS = company submission; KM = Kaplan-Meier

Endometrial
As of OCT-2021 data cut-off, death events occurred in 32 (38.6%) participants. Median OS was not reached (95% confidence interval (CI): 48.0, not reached (NR)) with 67.2% of participants being still alive at 24 months.

Gastric
As of OCT-2021 data cut-off, death events occurred in 29 (56.9%) participants. Median OS was 26.9 months (95% CI: 6.6, NR) with 50.0% of participants being still alive at 24 months.

Small intestine
As of OCT-2021 data cut-off, death events occurred in 10 (37.0%) participants. Median OS was not reached (95% CI: 16.2, NR) with 62.7% of participants being still alive at 24 months.

Biliary
As of OCT-2021 data cut-off, death events occurred in 16 (72.7%) participants. Median OS was 19.4 months (95% CI: 6.5,44.8) with 50.0% of participants being still alive at 24 months.

3.2.5.1.2 KEYNOTE-164

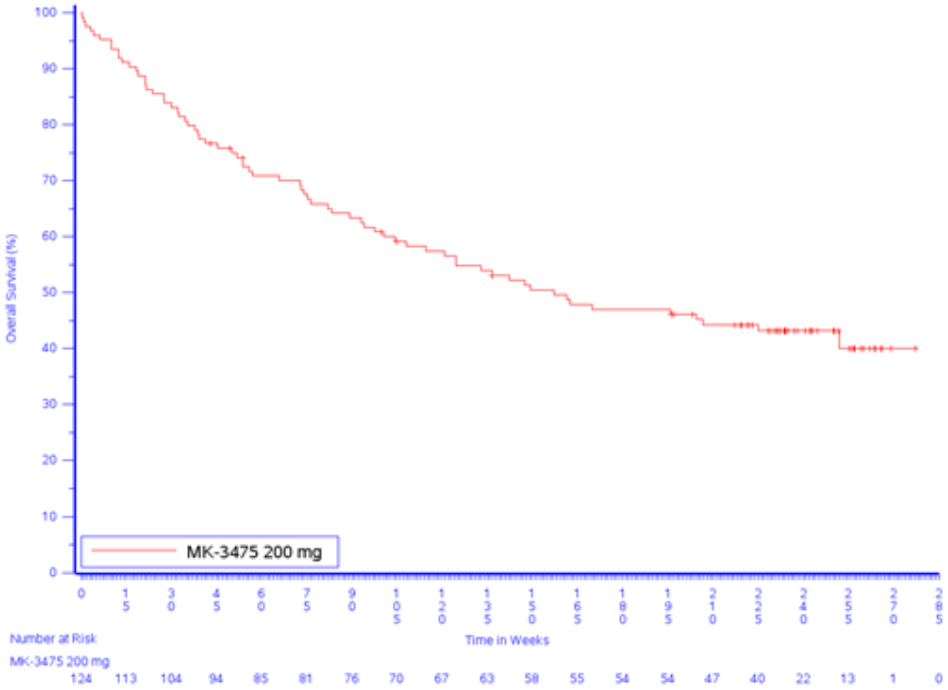
In the all subjects as treated (ASaT) population, treatment with pembrolizumab suggested a prolonged benefit with respect to OS. As of FEB-2021 data cut-off, death events occurred in 69 (55.6%) participants. The median OS was 36.1 months (95% CI: 24.0, NR) with more than 50% of participants being still alive at 36 months.

Table 3.26: Estimated median and mean of overall survival – Pooled Cohorts A and B (ASaT population)

Study: KEYNOTE-164 Treatment	N	Number of Events (%)	Est. Median Time in Weeks	95% CI of Est. Median Time in Weeks	Est. Mean Time in Weeks	SE of Est. Mean Time in Weeks	95% CI of Est. Mean Time in Weeks
Pembrolizumab 200 mg Q3W	124	69 (55.6)	157.1	(104.3, -)	151.5	9.0	(133.8, 169.1)

Based on Table 19 of the CS[2]
Number of participants: all-subjects-as-treated population, Cohort A and Cohort B
Estimated median and mean time is from product-limit (Kaplan–Meier) method
Overall survival is defined as the time from first day of study treatment to death due to any cause
ASaT = all subjects as treated; CI = confidence intervals; CS = company submission; SE = standard error; Q3W = once every three weeks

Figure 3.2: KM estimates of overall survival – Pooled Cohorts A and B (ASaT population)



Based on Figure 6 of the CS[2]
ASaT = all subjects as treated; CS = company submission; KM = Kaplan-Meier

Table 3.27: Summary of overall survival – Pooled Cohorts A and B (ASaT population)

	Pembrolizumab 200 mg Q3W
Participants in population	124
Number (%) of Events	69 (55.6)
Person-Months	3985
Event Rate/100 Person-Months (%)	1.7
Median OS (Months)[§]	36.1
95% CI for Median OS[§]	(24.0)
OS rate at 12 Months in % [§]	74.2
OS rate at 24 Months in % [§]	59.1
OS rate at 36 Months in % [§]	50.5
OS rate at 48 Months in % [§]	44.3

Based on Table 20 of the CS[2]
[§] From product-limit (Kaplan–Meier) method for censored data.
ASaT = all subjects as treated; CI = confidence interval; CS = company submission; OS = Overall survival; Q3W = once every three weeks

3.2.5.2 Progression-free survival

3.2.5.2.1 KEYNOTE-158

Table 3.28 shows PFS results by tumour site based on independent central radiologic review. Median PFS ranged from 4.1 (gastric) to 23.4 (small intestine). At 24 months, more than 30% of participants in each tumour site had not progressed, by Kaplan-Meier (KM) estimation.

Table 3.28: Summary of PFS based on RECIST 1.1 per central radiology assessment by tumour site (ASaT population for efficacy analysis)

Study: KEYNOTE-158	Endometrial (N=83)	Gastric (N=51)	Cholangiocarcinoma (N=22)	Small intestine (N=27)
Number (%) of PFS events	51 (61.4)	33 (64.7)	18 (81.8)	14 (51.9)
Person-months	1,352	795	304	632
Event rate/100 person-months (%)	3.8	4.2	5.9	2.2
Median PFS (months)[a]	13.1	4.1	4.2	23.4
95% CI for median PFS[a]	(4.9, 25.7)	(2.1, 24.6)	(2.1, 24.9)	(4.3, NR)
PFS rate at 6 months in % [a]	60.0	47.1	45.5	70.4
PFS rate at 12 months in % [a]	50.9	41.1	36.4	58.8
PFS rate at 18 months in % [a]	44.8	38.5	31.8	58.8
PFS rate at 24 months in % [a]	39.0	38.5	31.8	49.8

Based on Table 24 of the CS[2]

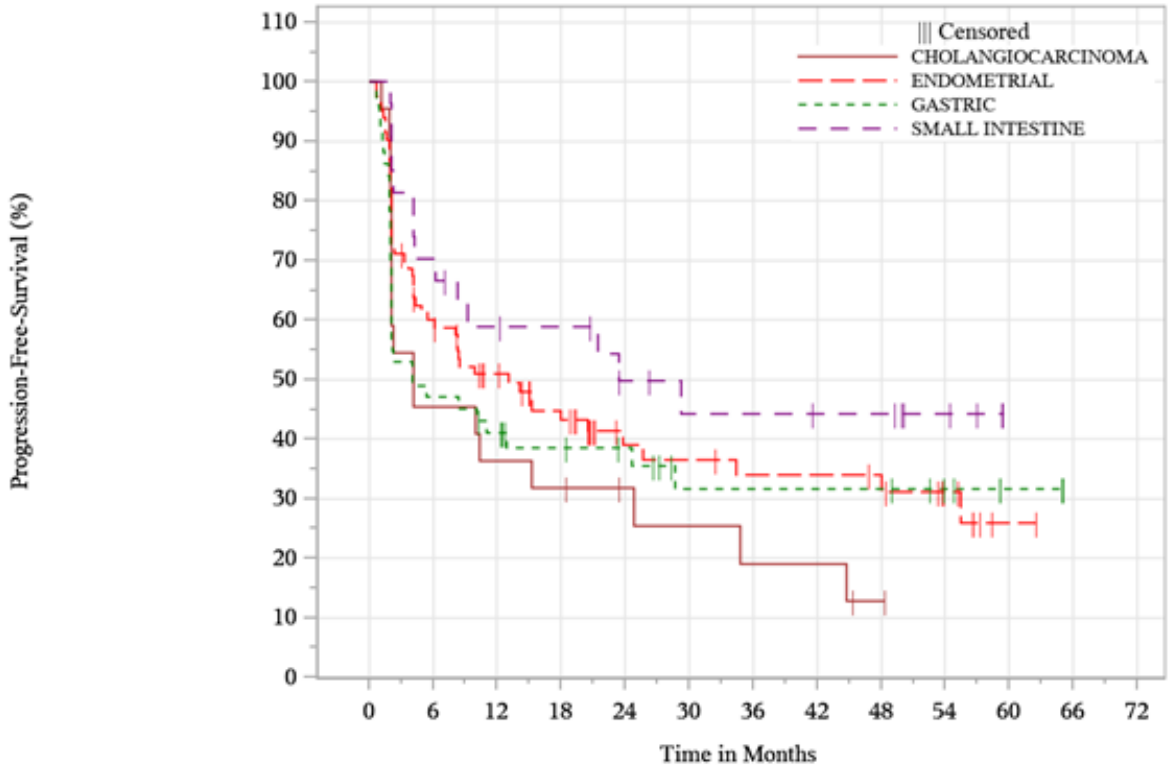
Progression-free survival is defined as time from date of first dose to disease progression, or death, whichever occurs first;

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

Participants who received at least one dose of pembrolizumab in KN158 with MSI-H tumours in cohort K with 6 months follow-up are included.

ASaT = all subjects as treated; CS = company submission; MSI-H = microsatellite instability-high; NR = not reached; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours

Figure 3.3: KM estimates of PFS based on RECIST1.1 per central radiology assessment by tumour site (ASaT population for efficacy analysis)



n at risk

CHOLANGIOCARCINOMA	22	10	8	7	5	4	3	3	1	0	0	0	0
ENDOMETRIAL	83	48	36	28	16	15	13	13	12	7	1	0	0
GASTRIC	51	24	20	15	13	8	8	8	8	5	2	0	0
SMALL INTESTINE	27	19	15	14	10	8	8	7	7	4	0	0	0

Based on Figure 9 of the CS[2]
ASaT = all subjects as treated; CS = company submission; KM = Kaplan-Meier; RECIST = Response Evaluation Criteria in Solid Tumours

Endometrial

As of OCT-2021 data cut-off, events were observed in 51 (61.4%) participants. Median PFS was 13.1 months (95% CI: 4.9, 25.7) with 39% of participants being still progression-free (PF) at 24 months, by KM estimation.

Gastric

As of OCT-2021 data cut-off, events were observed in 33 (64.7%) participants. Median PFS was 4.1 months (95% CI: 2.1, 24.6) with 38.5% of participants being still PF at 24 months, by KM estimation.

Small intestine

As of OCT-2021 data cut-off, events were observed in 14 (51.9%) participants Median PFS was 23.4 months (95% CI: 4.3, NR) with 49.8% of participants being still PF at 24 months, by KM estimation.

Biliary

As of OCT-2021 data cut-off, events were observed in 18 (81.8%) participants. Median PFS was 4.2 months (95%-CI: 2.1, 24.9) with 31.8% of participants being still PF at 24 months, by KM estimation.

3.2.5.2.2 KEYNOTE-164

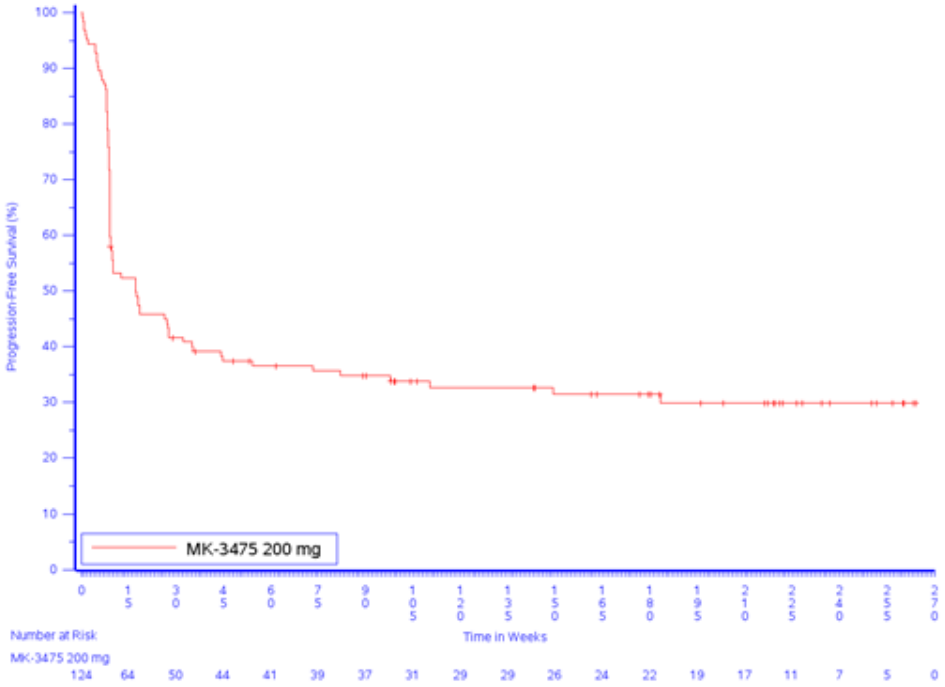
Table 3.29 shows PFS results in the ASaT population based on independent central radiologist review. As of the February 2021 data cut-off, PFS events were observed in 84 (67.7%) participants. Median PFS was 4.0 months (95% CI: 2.1, 7.4). At 36 months, more than 30% of participants had not progressed.

Table 3.29: Estimated median and mean of PFS based on RECIST 1.1 per central radiology assessment – Pooled Cohorts A and B (ASaT population)

Study: KEYNOTE-164 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 200 mg Q3W	124	84 (67.7)	17.3	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 17 of the CS2
Number of participants: all-participants-as-treated population, Cohort A and Cohort B
Cohort A: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least two lines of standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan
Cohort B: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least one line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody)
Estimated median and mean time is from product-limit (Kaplan–Meier) method
Progression-free survival is defined as the time from first day of study treatment to the first documented disease progression (based on IRC assessment) or death due to any cause, whichever occurs first
ASaT = all subjects as treated; CI = confidence interval; CRC = colorectal cancer; CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EGFR = epidermal growth factor receptor; IRC = independent radiologist review committee; MSI-H = microsatellite instability-high; PFS = progression-free survival; Q3W = once every three weeks; RECIST = Response Evaluation Criteria in Solid Tumours; SE = standard error; VEGF = vascular endothelial growth factor

Figure 3.4: KM estimates of PFS based on RECIST 1.1 per central radiology assessment – Pooled Cohorts A and B (ASaT population)



Based on Figure 5 of the CS[2]

ASaT = all subjects as treated; CS = company submission; KM = Kaplan-Meier; RECIST = Response Evaluation Criteria in Solid Tumours

Table 3.30: Summary of PFS based on IRC assessment per RECIST 1.1 – Pooled Cohorts A and B (ASaT population)

Study: KEYNOTE-164	Pembrolizumab 200mg Q3W
Participants in population	124
Number (%) of PFS Events	84 (67.7)
Person-Months	1924
Event Rate/100 Person-Months (%)	4.4
Median PFS (Months)§	4.0
95% CI for Median PFS§	[redacted]
PFS rate at 6 Months in % §	45.8
PFS rate at 12 Months in % §	37.5
PFS rate at 24 Months in % §	33.8
PFS rate at 36 Months in % §	31.5

Based on Table 18 of the CS2

Progression-free survival is defined as time from first day of study treatment to disease progression, or death, whichever occurs first.

§ From product-limit (Kaplan–Meier) method for censored data.

ASaT = all subjects as treated; CI = confidence interval; CS = company submission; IRC = independent radiologist review committee; PFS = progression-free survival; Q3W = once every three weeks; RECIST = Response Evaluation Criteria in Solid Tumours

3.2.5.3 Response Rate

3.2.5.3.1 KEYNOTE-158

Objective response rate (ORR) data by tumour site for the participants that have been followed for 6 months prior to data cut-off (ASaT population for efficacy analysis) are provided in Table 3.31. Pembrolizumab monotherapy provided clinically meaningful anticancer activity with respect to ORR across the four tumour sites ([redacted]%, 95%CI: [redacted], [redacted]).

Table 3.31: Summary of best objective response based on RECIST 1.1 per central radiology assessment by tumour site (ASaT population for efficacy analysis)

Tumour site	N	Objective response (CR+PR)	Complete response (CR)	Partial response (PR)	Stable disease (SD)	Disease control (CR+PR+SD)	Progressive disease (PD)	Non-evaluable (NE)	No assessment
		n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]	n (%) 95% CI[a]
Endometrial	83	42 (50.6) (39.4, 61.8)	13 (15.7) (8.6, 25.3)	29 (34.9) (24.8, 46.2)	16 (19.3) (11.4, 29.4)	58 (69.9) (58.8, 79.5)	22 (26.5) (17.4, 37.3)	1 (1.2) (0.0, 6.5)	2 (2.4) (0.3, 8.4)
Gastric	51	19 (37.3) (24.1, 51.9)	7 (13.7) (5.7, 26.3)	12 (23.5) (12.8, 37.5)	7 (13.7) (5.7, 26.3)	26 (51.0) (36.6, 65.2)	18 (35.3) (22.4, 49.9)	1 (2.0) (0.0, 10.4)	6 (11.8) (4.4, 23.9)
Small intestine	27	15 (55.6) (35.3, 74.5)	4 (14.8) (4.2, 33.7)	11 (40.7) (22.4, 61.2)	6 (22.2) (8.6, 42.3)	21 (77.8) (57.7, 91.4)	5 (18.5) (6.3, 38.1)	0 (0.0) (0.0, 12.8)	1 (3.7) (0.1, 19.0)
Cholangiocarcinoma	22	9 (40.9) (20.7, 63.6)	3 (13.6) (2.9, 34.9)	6 (27.3) (10.7, 50.2)	3 (13.6) (2.9, 34.9)	12 (54.5) (32.2, 75.6)	8 (36.4) (17.2, 59.3)	0 (0.0) (0.0, 15.4)	2 (9.1) (1.1, 29.2)

Based on Table 22 of the CS[2]

[a] Based on binomial exact confidence interval method. Only confirmed responses are included.

'No Assessment' (NA) counts participants who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cut-off date including missing, discontinuing or death before the first post-baseline scan.

ASaT = all subjects as treated; CI = confidence interval; CR = complete response; CS = company submission; NE = non-estimable; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease

Figure 3.5: Forest plot of objective response rate by tumour site based on RECIST 1.1 per central radiology assessment (ASaT population for efficacy analysis)

Note: Only confirmed responses are included.
ASaT = all subjects as treated; CS = company submission; KM = Kaplan-Meier; RECIST = Response Evaluation Criteria in Solid Tumours

Endometrial

Among the 83 participants with MSI-H endometrial tumours, 42 participants achieved an independent radiologist review committee (IRC)-confirmed objective response, resulting in an ORR of 50.6% (95% CI: 39.4, 61.8); complete response (CR) was achieved in 15.7% (95% CI: 8.6, 25.3) of participants. Disease control was achieved in 69.9% (95%CI: 58.8, 79.5) of participants.

Gastric

Among the 51 participants with MSI-H gastric tumours, 19 participants achieved an IRC-confirmed objective response, resulting in an ORR of 37.3% (95% CI: 24.1, 51.9); CR was achieved in 13.7% (95% CI: 5.7, 26.3) of participants. Disease control was achieved in 51.0% (95%CI: 36.6, 65.2) of participants.

Small intestine

Among the 27 participants with MSI-H small intestine tumours, 15 participants achieved an IRC-confirmed objective response, resulting in an ORR of 55.6% (95% CI: 35.3, 74.5); CR was achieved in 14.8% (95% CI: 4.2, 33.7) of participants. Disease control was achieved in 77.8% (95%CI: 57.7, 91.4) of participants.

Biliary

Among the 22 participants with MSI-H biliary tumours, nine participants achieved an IRC-confirmed objective response, resulting in an ORR of 40.9% (95% CI: 20.7, 63.6); CR was achieved in 13.6% (95% CI: 2.9, 34.9) of participants. Disease control was achieved in 54.5% (95%CI: 32.2, 75.6) of participants.

3.2.5.3.2 KEYNOTE-164

In the ASaT population, pembrolizumab monotherapy provided clinically meaningful anticancer activity with respect to ORR. Forty-two participants achieved an IRC-confirmed objective response, resulting in an ORR of 33.9% (95% CI: 25.6, 42.9); CR was achieved in 9.7% (95% CI: 5.1, 16.3) of participants. Disease control was achieved in 53.2% (95% CI: 44.1, 62.2) of participants.

Table 3.32: Summary of best objective response based on RECIST 1.1 per central radiology assessment – Pooled Cohorts a and B (ASaT population)

Study: KEYNOTE-164	**Total, N=124**	
Response evaluation	**n**	**Percentage (95 %-CI)**
Objective response (CR+PR)	42	33.9 (25.6; 42.9)
Complete response (CR)	12	9.7 (5.1; 16.3)
Partial response (PR)	30	24.2 (17.0; 32.7)
Stable disease (SD)	24	19.4 (12.8; 27.4)
Disease control (CR+PR+SD)	66	53.2 (44.1; 62.2)
Progressive disease (PD)	53	42.7 (33.9; 51.9)
Non-evaluable (NE)	5	4.0 (1.3; 9.2)

Based on Table 15 of the CS[2]
Only confirmed responses are included
Based on binomial exact confidence interval method
Number of participants: all-subjects-as-treated population, Cohort A and Cohort B
Cohort A: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least 2 lines of standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan
Cohort B: participants with locally advanced unresectable or metastatic dMMR or MSI-H CRC who have been previously treated with at least 1 line of systemic standard of care therapy (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody)
ASaT = all subjects as treated; CI = confidence interval; CR = complete response; CRC = colorectal cancer; CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EGFR = epidermal growth factor receptor; MSI-H = microsatellite instability-high; NE = non-estimable; PR = partial response; SD = stable disease; VEGF = vascular endothelial growth factor

3.2.5.4 Duration of response

3.2.5.4.1 KEYNOTE-158

Among responders, treatment with pembrolizumab produced durable responses across the four tumour sites, with more than 40% of responders in each tumour site having an extended response duration of ≥36 months, by KM estimation. Median DOR was not reached for any of the tumour sites, except for biliary. Time to response and duration of response by tumour site are provided in Table 3.33.

Table 3.33: Summary of time to response and duration of response based on RECIST 1.1 per central radiology assessment by tumour site in participants with confirmed response (ASaT population for efficacy analysis)

Study: KEYNOTE-158	Endometrial (N=83)	Gastric (N=51)	Cholangiocarcinoma (N=22)	Small intestine (N=27)
Number of participants with response[a]	42	19	9	15
Time to Response (months)				
Mean (SD)	3.5 (2.6)	3.5 (1.5)	3.0 (1.1)	4.2 (4.7)
Median (Range)	2.1 (1.3-12.7)	3.8 (1.9-6.5)	2.4 (1.9-4.2)	2.1 (1.9-17.9)
Response Duration[b] (months)				
Median (Range)	NR (2.9 - 60.4+)	NR (6.2 - 63.0+)	30.6 (6.2 - 46.0+)	NR (3.7+ - 57.3+)
Number (%[b]) of Participants with Extended Response Duration:				
≥6 months	38 (90.4)	19 (100.0)	9 (100.0)	12 (92.9)
≥12 months	29 (84.9)	13 (89.5)	8 (88.9)	10 (92.9)
≥18 months	16 (65.4)	12 (89.5)	6 (77.8)	9 (83.6)
≥24 months	13 (65.4)	10 (81.3)	4 (62.2)	7 (73.1)
≥36 months	11 (59.9)	8 (81.3)	2 (41.5)	7 (73.1)

Based on Table 23 of the CS[2]

[a] Includes participants with confirmed complete response or partial response.

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

"+" indicates there is no progressive disease by the time of last disease assessment.

ASaT = all subjects as treated; CS = company submission; NR = not reached; RECIST = Response Evaluation Criteria in Solid Tumours; SD = standard deviation

Endometrial

As of OCT-2021 data cut-off, median DOR was not reached (range: 2.9-60.4+ months, where "+" indicates an ongoing response as of the data cut-off date). By KM estimation, 59.9% of responders have an extended response duration of ≥36 months.

Gastric

As of OCT-2021 data cut-off, median DOR was not reached (range: 6.2-63.0+ months, where "+" indicates an ongoing response as of the data cut-off date). By KM estimation, 81.3% of responders have an extended response duration of ≥36 months.

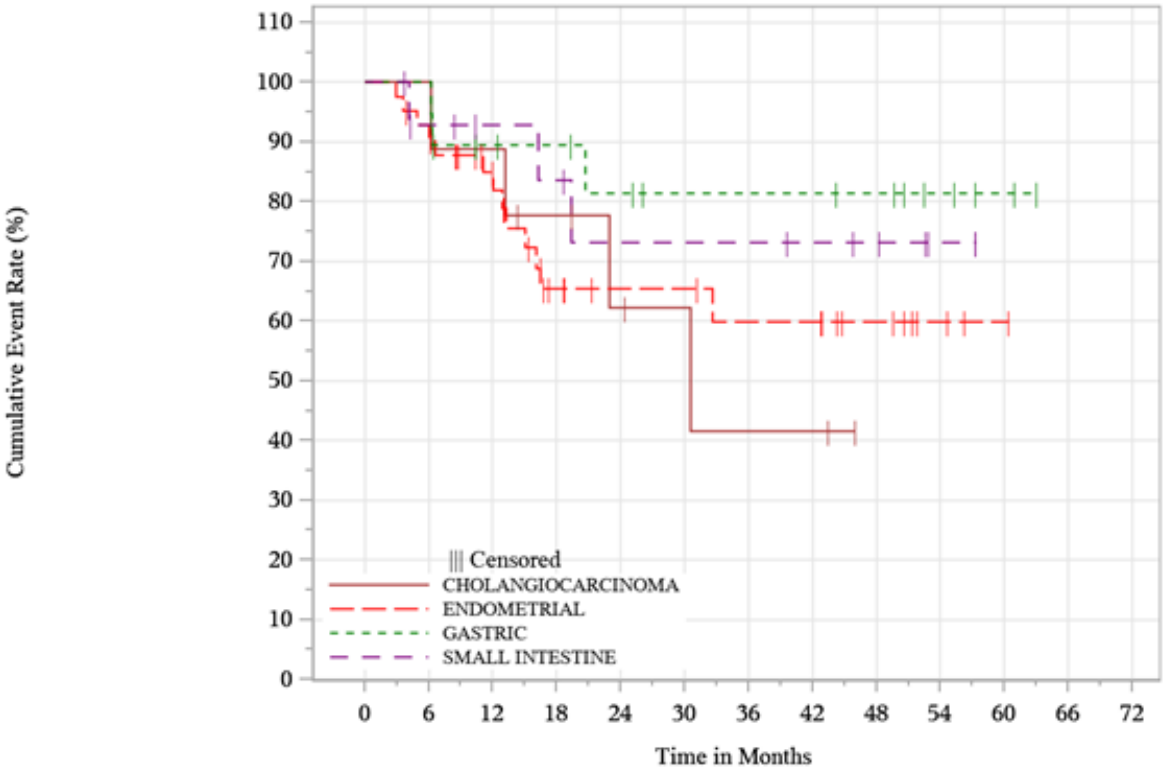
Small intestine

As of OCT-2021 data cut-off, median DOR was not reached (range: 3.7+ -57.3+ months, where "+" indicates an ongoing response as of the data cut-off date). By KM estimation, 73.1% of responders have an extended response duration of ≥36 months.

Biliary

As of OCT-2021 data cut-off, median DOR was 30.6 (range: 6.2 - 46.0+ months, where "+" indicates an ongoing response as of the data cut-off date). By KM estimation, 41.5% of responders have an extended response duration of ≥36 months.

Figure 3.6: KM estimates of objective response duration based on RECIST 1.1 per central radiology assessment in participants with confirmed response (ASaT population for efficacy analysis)



n at risk

CHOLANGIOCARCINOMA	9	9	8	6	4	3	2	2	0	0	0	0	0
ENDOMETRIAL	42	38	29	16	13	13	11	11	7	3	1	0	0
GASTRIC	19	19	13	12	10	8	8	8	7	4	2	0	0
SMALL INTESTINE	15	12	10	9	7	7	7	6	5	2	0	0	0

Based on Figure 8 of the CS[2]
ASaT = all subjects as treated; CS = company submission; KM = Kaplan-Meier; RECIST = Response Evaluation Criteria in Solid Tumours

3.2.5.4.2 KEYNOTE-164

Among participants who achieved a response (n=42), treatment with pembrolizumab produced durable responses, with >90% of responders having an ongoing response for ≥156 weeks, by KM estimation. As of FEB-2021 data cut-off, median DOR was not reached (range: 19.3-254.4+ weeks, where "+" indicates an ongoing response as of the data cut-off date). Time to response and duration of response are provided in Table 3.34.

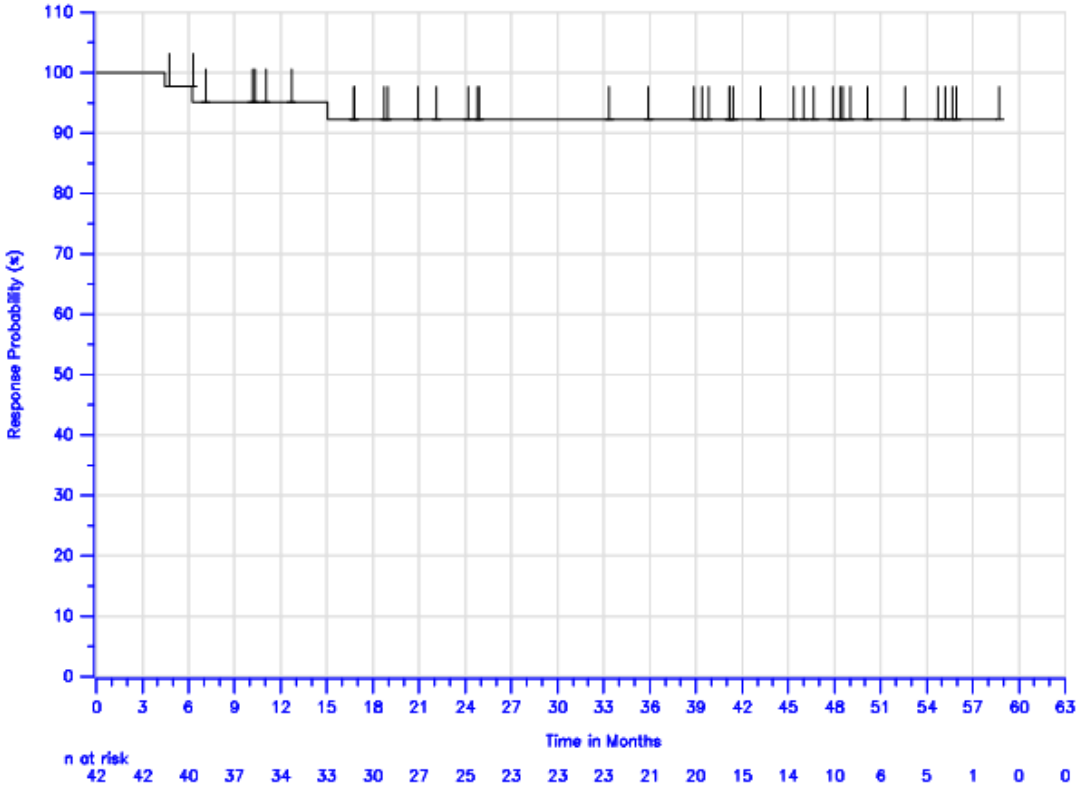
Table 3.34: Summary of time to response and response duration in participants with confirmed response based on RECIST 1.1 per central radiology assessment – Pooled Cohorts A and B (ASaT population)

Study: KEYNOTE-164	Total, N=124
Number of participants with response[†]	42

Study: KEYNOTE-164	Total, N=124
Time to Response (weeks)	
Mean (SD)	27.0 (27.6)
Median (Range)	17.9 (7.9-136.1)
Response Duration‡ (weeks)	
Median (Range)	NR (19.3 - 254.4+)
Number (%‡) of Participants with Extended Response Duration:	
≥26 weeks	40 (97.6)
≥52 weeks	34 (95.1)
≥78 weeks	30 (92.2)
≥104 weeks	26 (92.2)
≥156 weeks	21 (92.2)

Based on Table 16 of the CS[2]
Number of participants: all-subjects-as-treated population, Cohort A and Cohort B
† Includes participants 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.
ASaT = all subjects as treated; CS = company submission; NR = Not Reached; RECIST = Response Evaluation Criteria in Solid Tumours; SD = Standard Deviation

Figure 3.7: KM estimates of objective response (confirmed) duration based on RECIST 1.1 per central radiology assessment – Pooled Cohorts A and B (ASaT population)



Based on Figure 4 of the CS[2]
Database cut-off date: 19 February 2021
ASaT = all subjects as treated; CS = company submission; KM = Kaplan-Meier; RECIST = Response Evaluation Criteria in Solid Tumours

3.2.6.5 Health-related quality of life

3.2.5.5.1 KEYNOTE-158

No patient-reported outcomes (PROs) were collected at the time of 15-OCT-2021 data cut-off. Data reported below were collected in previous data cut-off (05-OCT-2020 – IA11) and were pooled to include participants with the four tumour types from Cohort K relevant to this appraisal.

Patient-reported outcomes were evaluated using the European Organisation for the Research and Treatment of Cancer - Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the EuroQol 5D quality of life instrument (EQ-5D) questionnaires. The analysis for PROs is based on the full analysis set (FAS) population with both baseline and post-baseline measurements. The data are presented without imputation for missing data.

EQ-5D

Both the EQ-5D health utility score and visual analogue scale (VAS) scores were measured. Completion rates were [redacted]% and [redacted]% at baseline and Week 9, respectively. Compliance rates were [redacted]% and [redacted]% at baseline and Week 9, respectively.

EQ-5D health utility score

At Week 9, an improvement in the EQ-5D health utility score from baseline across all participants was observed (mean change = [redacted] points; 95% CI: [redacted]). Among participants who achieved CR/PR, analysis of the EQ-5D health utility score showed a [redacted] change from baseline with a mean change of [redacted] points (95% CI: [redacted]) (Table 3.35).

Table 3.35: Summary of mean change from baseline to Week 9 in EQ-5D utility score (FAS population)

Endpoint	Treatment	N	Baseline Mean (SD)	Week 9 Mean (SD)	Change from baseline to Week 9 Mean (95% CI)
European utility value rescaled with the mean value for dead	All participants	[redacted]	[redacted]	[redacted]	[redacted]
	Participants who responded (CR+PR)	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with stable disease	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with PD	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 26 of the CS[2]
N is the number of participants in each treatment group with non-missing change from baseline at the specific time point.
CI = confidence interval; CR = complete response; CS = company submission; FAS = full analysis set; NE = non-estimable; PR = partial response; SD = standard deviation; PD = progressive disease

EQ-5D VAS scores

EQ-5D VAS scores across all participants improved from baseline to Week 9 (mean change=[redacted] points; 95% CI: [redacted]). Among participants who achieved CR/PR, an improvement in EQ-5D VAS score

was observed with a mean change from baseline of [redacted] points (95% CI: [redacted]) (Table 3.36). EQ-5D VAS score over time was stable or improved from baseline through Week 11.

Table 3.36: Summary of mean change from baseline to Week 9 in EQ-5D VAS (FAS population)

Endpoint	Treatment	N	Baseline Mean (SD)	Week 9 Mean (SD)	Change from Baseline to Week 9 Mean (95% CI)
EQ-5D VAS score	All participants	[redacted]	[redacted]	[redacted]	[redacted]
	Participants who responded (CR+PR)	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with stable disease	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with PD	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 26, CS[2]
N is the number of participants in each treatment group with non-missing change from baseline at the specific time point.
Database cut-off date: 05OCT2020
CI = confidence interval; CR = complete response; CS = company submission; EQ-5D = EuroQol 5D quality of life instrument; FAS = full analysis set; PR = partial response; SD = standard deviation; PD = progressive disease; VAS = visual analogue scale

Figure 3.8: Mean change from baseline and 95% CI for the EORTC EQ-5D VAS over time (FAS population)

Based on Figure 11 of the CS[2]
Database cut-off date: 05 October 2020
CI = confidence interval; CS = company submission; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer - Quality of Life Questionnaire C30; FAS = full analysis set; Q3W = once every three weeks; VAS = visual analogue scale

EORTC QLQ-C30

Completion rates were [redacted]% and [redacted]% at baseline and Week 9, respectively. Compliance rates were [redacted]% and [redacted]% at baseline and Week 9, respectively.

Overall, pembrolizumab monotherapy showed improvement in the majority of EORTC QLQ-C30 scores across all participants, with [redacted] improvements among participants who achieved CR/PR. EORTC global health status/QoL scores across all participants improved from baseline to Week 9 (mean change=[redacted], 95% CI: [redacted]). [redacted] improvements were observed among participants who achieved CR/PR, with a mean change from baseline in global health score of [redacted] points (95% CI: [redacted]) (Table 3.37). However, because of the single-arm design of this study, the interpretability of the PRO results is limited.

Table 3.37: Summary of Mean Change from Baseline to Week 9 in EORTC QLQ-C30 Global Health Status/QoL (Cholangiocarcinoma, Endometrial, Gastric, Small Intestine) (FAS Population: Participants with Baseline and Post-Baseline Measurements)

Endpoint	Treatment	N	Baseline Mean (SD)	Week 9 Mean (SD)	Change from Baseline to Week 9 Mean (95% CI)
Global health status/QoL	All Participants	[redacted]	[redacted]	[redacted]	[redacted]
	Participants who responded (CR+PR)	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with stable disease	[redacted]	[redacted]	[redacted]	[redacted]
	Participants with PD	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 165 of the CS appendices[9]

N is the number of participants in each treatment group with non-missing change from baseline at the specific time point.

CI = confidence interval; CR = complete response; CS = company submission; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer - Quality of Life Questionnaire C3; FAS = full analysis set; NE = non-estimable; PD = progressive disease; PR = partial response; QoL = quality of life; SD = standard deviation

EORTC QLQ-C30 global health status/QoL score over time was stable or improved from baseline through Week 111 (Figure 3.9).

[redacted]

[redacted]

Functional scale scores across all participants improved from baseline to Week 9 for [redacted]. Mean score change from baseline to Week 9 was stable for [redacted] (Figure 3.10).

Figure 3.10: Change from Baseline to Week 9 and 95% CI in EORTC QLQ-30 Functional Scale/Global Health Status/QoL (by Response) (Cholangiocarcinoma, Endometrial, Gastric, Small Intestine) (FAS Population: Participants with Baseline and Post-Baseline Measurements)

Based on Figure 70 of the CS appendices[9]
CI = confidence interval; CR = complete response; CS = company submission; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer - Quality of Life Questionnaire C3; FAS = full analysis set; HRQoL = health-related quality of life; PD = progressive disease; PR = partial response; QoL = quality of life; SD = stable disease

3.2.5.5.2 KEYNOTE-164

No data collected for this outcome

3.2.5.6 Additional data collection for KEYNOTE-158

An additional interim analysis was performed (IA14 - database cut-off date: 12-JAN-2022), corresponding to an additional 3-month follow-up, as a response to an FDA request. Compared to 15-OCT-2021 data cut-off, [redacted] additional PFS event had occurred only (endometrial cancer subgroup) and [redacted] OS events ([redacted] in endometrial, [redacted] in gastric and [redacted] in biliary subgroup) were reported for the tumour sites relevant to this appraisal. [redacted]. Overall, the results from latest data-cut are consistent with the results previously presented.

A summary results table comparing the results from the two data cut-off dates is provided below (Table 3.38).

Table 3.38: Summary of efficacy results from OCT-2021 and JAN-2022 data cut-off

	Database cut-off date (15-OCT-2021)	Database cut-off date (12-JAN-2022)
Endometrial		
ORR, % (95% CI)	50.6 (39.4, 61.8)	[redacted]
Number (%) of PFS events	51 (61.4)	[redacted]
Median PFS, months (95% CI)	13.1 (4.9, 25.7)	[redacted]
PFS rate, % at 24 Months	39.0	[redacted]
Number (%) of OS events	32 (38.6)	[redacted]
Median OS, months (95% CI)	NR (48.0, NR)	[redacted]
OS rate, % at 24 Months	67.2	[redacted]
Gastric		
ORR, % (95% CI)	37.3 (24.1, 51.9)	[redacted]
Number (%) of PFS events	33 (64.7)	[redacted]
Median PFS, months (95% CI)	4.1 (2.1, 24.6)	[redacted]
PFS rate, % at 24 Months	38.5	[redacted]
Number (%) of OS events	29 (56.9)	[redacted]
Median OS, months (95% CI)	26.9 (6.6, NR)	[redacted]
OS rate, % at 24 Months	50.0	[redacted]
Small intestine		
ORR, % (95% CI)	55.6 (35.3, 74.5)	[redacted]
Number (%) of PFS events	14 (51.9)	[redacted]
Median PFS, months (95% CI)	23.4 (4.3, NR)	[redacted]
PFS rate, % at 24 Months	49.8	[redacted]
Number (%) of OS events	10 (37.0)	[redacted]
Median OS, months (95% CI)	NR (16.2, NR)	[redacted]
OS rate, % at 24 Months	62.7	[redacted]
Biliary cancer		
ORR, % (95% CI)	40.9 (20.7, 63.6)	[redacted]
Number (%) of PFS events	18 (81.8)	[redacted]
Median PFS, months (95% CI)	4.2 (2.1, 24.9)	[redacted]
PFS rate, % at 24 Months	31.8	[redacted]
Number (%) of OS events	16 (72.7)	[redacted]
Median OS, months (95% CI)	19.4 (6.5, 44.8)	[redacted]
OS rate, % at 24 Months	50.0	[redacted]

Based on Table 28 of the CS[2]
CI = confidence interval; CS = company submission; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

3.2.5.7 Subgrouping

3.2.5.7.1 KEYNOTE-158

Subgrouping for tumour site was carried out in accordance with the NICE scope. However, because an overall analysis was not carried out for KEYNOTE-158, all the results already given in Section 3.2.6 for KEYNOTE-158 are subgrouped for tumour site.

Subgrouping by previous therapy was not carried out.

3.2.5.7.2 KEYNOTE-164

KEYNOTE-164 was only concerned with colorectal tumours and so no subgrouping by tumour site was necessary.

Subgrouping by previous therapy was not carried out.

3.2.6 Adverse events

3.2.6.1 KEYNOTE-158

AEs as observed at the latest data-cut (data cut-off date of 12-JAN-2022) for the population in Cohort K in the four tumour sites relevant for this appraisal (endometrial, gastric, small intestine and biliary), are provided in this section. Further details of AEs are available in Appendix F.

Among the participants who had at least 1 dose of pembrolizumab [redacted] participants had at least one AE of any grade regardless of relationship to study intervention. [redacted] participants experienced a Grade 3 to 5 AE related to study intervention and [redacted] participants discontinued from study intervention due to an AE related to study intervention (Table 3.39).

Table 3.39: Adverse event summary (ASaT population)

Study: KEYNOTE-158	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	[redacted]	
with one or more adverse events		[redacted]
with no adverse event	[redacted]	
with drug-related[a] adverse events		[redacted]
with toxicity grade 3-5 adverse events	[redacted]	
with toxicity grade 3-5 drug-related adverse events		[redacted]
with serious adverse events	[redacted]	
with serious drug-related adverse events		[redacted]
who died	[redacted]	
who died due to a drug-related adverse event		[redacted]
discontinued drug due to an adverse event	[redacted]	
discontinued drug due to a drug-related adverse event		[redacted]
discontinued drug due to a serious adverse event	[redacted]	
discontinued drug due to a serious drug-related adverse event		[redacted]

Based on Table 37 of the CS[2]
(Database Cut-off date: 12JAN2022).
[a] Determined by the investigator to be related to the drug.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
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.
ASaT = all subjects as treated; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; Q3W = once every three weeks

The most frequently reported AEs (incidence ≥20%) were diarrhoea, fatigue, pruritus, arthralgia, nausea and vomiting (Table 3.40). The majority of these events were Grade 1 or 2 in severity.

Table 3.40: Participants with adverse events by decreasing incidence (incidence ≥ 10%) (ASaT population)

Study: KEYNOTE-158	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	[redacted]	
with one or more adverse events		[redacted]
with no adverse events	[redacted]	
Diarrhoea		[redacted]

Study: KEYNOTE-158	Pembrolizumab 200 mg Q3W	
	n	(%)
Fatigue	[redacted]	[redacted]
Pruritus		
Arthralgia		
Nausea		
Vomiting		
Asthenia		
Constipation		
Decreased appetite		
Anaemia		
Abdominal pain		
Rash		
Alanine aminotransferase increased		
Aspartate aminotransferase increased		
Back pain		
Pyrexia		
Urinary tract infection		
Hypothyroidism		
Dyspnoea		

Based on Table 38 of the CS[2]
(Database cut-off date: 12JAN2022).
Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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.
ASaT = all subjects as treated; CS = company submission; Q3W = once every three weeks

Per investigator assessment, [redacted] of participants had one or more AEs that was related to pembrolizumab. The majority of these events were Grade 1 or 2 in severity. The most frequently reported drug-related AEs (≥10%) were pruritus, fatigue, diarrhoea, arthralgia, rash, and hypothyroidism (Appendix F).

A total of [redacted] participants had one or more Grade 3 to 5 AEs. The most frequently reported (≥2%) Grade 3 to 5 AEs were anaemia, blood alkaline phosphatase increased, aspartate aminotransferase increased, hyperglycaemia, and transaminases increased (Appendix F). The company stated that these events were consistent with the established safety profile of pembrolizumab monotherapy and with the underlying malignancies in patients with MSI-H tumours.

Per investigator assessment, [redacted] participants had 1 or more Grade 3 to 5 AEs that was related to study intervention (Appendix F).

[redacted] participants had an AE that resulted in death. Two participants suffered cardiac failure, and one participant each had Guillain-Barre syndrome, general physical health deterioration, malabsorption, myocarditis, and pneumonia (Appendix F). Per investigator assessment, [redacted] deaths were reported to be drug-related.

[redacted] participants had one or more SAEs. The most frequently reported SAEs were cholangitis and sepsis. Additional SAEs occurring at ≥1 % incidence are provided in Appendix F. Per investigator assessment, a total of [redacted] participants had one or more drug-related SAEs that occurred up to 90 days after the last dose of pembrolizumab (Appendix F).

Overall, [redacted] of participants had at least one adverse event of special interest (AEOSI) (Table 3.41) and [redacted] had at least one drug-related AEOSI. Most AEOSI were nonserious and manageable with standard clinical practice measures, such as systemic corticosteroids or hormone replacement and/or treatment interruption. The most frequently reported AEOSI (>1%) were hypothyroidism, hyperthyroidism, colitis, pneumonitis, hepatitis, infusion-related reaction, Guillain-Barre syndrome and interstitial lung disease (Appendix F).

Table 3.41: Adverse event summary AEOSI (ASaT population)

Study: KEYNOTE-158	Pembrolizumab 200mg Q3W	
	n	(%)
Participants in population	[redacted]	
with one or more adverse events	[redacted]	[redacted]
with no adverse event	[redacted]	
with drug-related[a] adverse events	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]
who died	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverse event	[redacted]	[redacted]

Based on Table 39 of the CS[2]
(Database cut-off date: 12JAN2022).
[a] Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
AEOSI = adverse events of special interest; ASaT = all subjects as treated; CS = company submission; Q3W = once every three weeks

EAG comment: Aggregation of data were not performed for the clinical efficacy outcomes from KEYNOTE-158, but the 4 tumour sites were combined for appraisal of specific AEs. It is possible that an aggregated result could obscure high levels of particular adverse events in a single tumour site. The company have been asked in the clarification letter to justify why aggregating results across tumour sites was deemed appropriate. The company responded with the following: "*In terms of adverse events, there was no "aggregation" or assumption of homogenous adverse event rates across tumour sites*". The EAG does not feel that this response justifies aggregation, because it does not demonstrate adverse event homogeneity across tumour types. Moreover, it denies that aggregation took place when aggregation is clearly apparent (although there are crude counts of the overall number of adverse events per tumour site, there are no data in the CS or Appendix F for specific adverse events that have been sub-grouped for tumour site). This has been deemed a key issue.

3.2.6.2 KEYNOTE-164

Adverse events as observed at FA (data cut-off date of 19-FEB-2021) are provided in this Section. Further details of AEs are available in Appendix F.

Among the participants included in the ASaT population, [redacted] participants had at least one AE of any grade regardless of relationship to study intervention. [redacted] participants experienced

a Grade 3 to 5 AE related to study intervention and [redacted] participants discontinued from study intervention due to an AE related to study intervention (Table 3.42).

Table 3.42: Adverse event summary (Pooled Cohorts A and B, ASaT population)

Study: KEYNOTE-164	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	[redacted]	
with one or more adverse events		
with no adverse event		
with drug-related† adverse events		
with toxicity grade 3-5 adverse events		
with toxicity grade 3-5 drug-related adverse events		
with serious adverse events		
with serious drug-related adverse events		
who died		
who died due to a drug-related adverse event		
discontinued‡ due to an adverse event		
discontinued due to a drug-related adverse event		
discontinued due to a serious adverse event		
discontinued due to a serious drug-related adverse event		

Based on Table 34 of the CS[2]
Database Cut-off date: 19FEB2021
† Determined by the investigator to be related to the drug.
‡ Study medication withdrawn.
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each participant will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
Grades are based on NCI CTCAE version 4.0.
ASaT = all subjects as treated; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; Q3W = once every three weeks; SAE = serious adverse event

The most frequently reported AEs (incidence ≥20%) were fatigue, diarrhoea, nausea, abdominal pain, vomiting, arthralgia, pyrexia and constipation (Table 3.43). The majority of these events were Grade 1 or 2 in severity.

Table 3.43: Participants with adverse events by decreasing incidence (incidence ≥10%) (Pooled Cohorts A and B, ASaT population)

Study: KEYNOTE-164	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	[redacted]	
with one or more adverse events		
with no adverse events		
Fatigue		
Diarrhoea		
Nausea		
Abdominal pain		
Vomiting		
Arthralgia		
Pyrexia		
Constipation		

Study: KEYNOTE-164	Pembrolizumab 200 mg Q3W	
	n	(%)
Anaemia		
Cough		
Decreased appetite		
Back pain		
Dyspnoea		
Oedema peripheral		
Asthenia		
Hypothyroidism		
Pruritus		
Rash		
Headache		
Upper respiratory tract infection		
Alanine aminotransferase increased		
Dyspepsia		

Based on Table 35 of the CS[2]
Database Cut-off date: 19FEB2021
Every participant is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.
MedDRA preferred terms 'Neoplasm Progression' ,'Malignant Neoplasm Progression' and 'Disease Progression' not related to the drug are excluded.
After the end of treatment, each participant will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.
ASaT = all subjects as treated; CS = company submission; Q3W = once every three weeks

Overall, [redacted] of participants reported at least 1 Grade 3 to 5 AE. The most frequently reported Grade 3 to 5 AEs (≥4% of participants) were anaemia, abdominal pain, alanine aminotransferase and aspartate aminotransferase increased, dyspnoea and sepsis (Appendix F).

[redacted] participants died due to AEs; these events were assessed as not related to study treatment by the investigator (Appendix F). [redacted] of participants reported at least one serious adverse event (SAE) (Appendix F).

[redacted] participants reported at least one AEOSI. The most frequently reported AEOSI (≥4% of participants) were hypothyroidism, hyperthyroidism and pneumonitis. [redacted] participants reported Grade 3-5 AEOSI of which [redacted] were assessed by the investigator as related to study treatment. [redacted] participants reported SAEs of which [redacted] were assessed as related to study treatment (Table 3.44). There were [redacted] Grade 4-5 AEOSI and no participants died due to an AEOSI (Appendix F).

Table 3.44: Adverse event summary AEOSI (Pooled Cohorts A and B, ASaT population)

Study: KEYNOTE-164	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population		
with one or more adverse events		
with no adverse event		
with drug-related† adverse events		
with toxicity grade 3-5 adverse events		
with toxicity grade 3-5 drug-related adverse events		
with serious adverse events		

Study: KEYNOTE-164	Pembrolizumab 200 mg Q3W
with serious drug-related adverse events	[redacted]
who died	
who died due to a drug-related adverse event	
discontinued‡ due to an adverse event	
discontinued due to a drug-related adverse event	
discontinued due to a serious adverse event	
discontinued due to a serious drug-related adverse event	

Based on Table 36 of the CS[2]

† Determined by the investigator to be related to the drug.

‡ Study medication withdrawn.

After the end of treatment, each participant will be followed for a minimum of 30 days for adverse event monitoring. SAE is monitored until 90 days after last dose.

AEs of special interest per ECI guidance. Q3W = once every three weeks

Grades are based on NCI CTCAE version 4.0.

Database Cut-off date: 19FEB2021

AE = adverse event; ASaT = all subjects as treated; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; ECI = event of clinical interest; NCI = National Cancer Institute; Q3W = once every three weeks; SAE = serious adverse event

3.2.7 Ongoing studies

KEYNOTE-164 is completed.

KEYNOTE-158 is still ongoing as additional patients will be recruited. Interim analysis 15 (IA15) is planned for different cohorts of the KEYNOTE-158 trial population (Cohort L and Cohort M), which are not relevant for the population of this appraisal. Further analysis for Cohort K will be conducted to meet regulatory requirements. However, timelines are currently unknown.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No description is given in the CS[2] about the specific methodology used to select the literature used in the ITC and the matching-adjusted indirect comparison (MAIC) (see section 3.4 for explanations of these terms). It appears likely, however, that the SLRs described in the CS appendices[9] (and described in Section 3.1 above) were the source of the literature. The literature included in the ITCs and MAIC are summarised in Table 3.45.

Table 3.45: Final comparators and associated studies – feasible ITC approaches

Tumour site	Comparator	Unadjusted ITC	MAIC	Included studies
CRC	Pooled FOLFOX/ FOLFIRI	X		Li 2018 Giantonio 2007 Cao 2015 Moore 2016 Xie 2014
	TAS-102	X		Yoshino 2012 Mayer 2015 Xu 2018
Endometrial	Chemotherapy (physician's choice of	X	X	Makker 2022

Tumour site	Comparator	Unadjusted ITC	MAIC	Included studies
	paclitaxel or doxorubicin)			
Gastric	FOLFIRI	X		Moehler 2016 Sym 2013
	Paclitaxel	X		Chao 2021
Small intestine	Nab-paclitaxel	X		Overman 2018
Cholangiocarcinoma	mFOLFOX	X		Choi 2021 Hwang 2015 Kim 2019
	mFOLFIRI	X		Choi 2021

Based on Table 29 of the CS[2]
CRC = colorectal cancer; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; (m)FOLFIRI = (modified) folinic acid, fluorouracil, irinotecan; mFOLFOX6 = modified folinic acid, fluorouracil, oxaliplatin; TAS-102 = tipiracil hydrochloride

EAG comment:

- The SLRs described in Section 3.1 appear to have been aimed at providing literature for the main clinical efficacy section. However, due to the possibility that no eligible comparative studies would be found it also appears that the SLRs were geared to additionally provide literature for a possible ITC, which is evidenced by the interventions comprising treatments other than pembrolizumab. As no comparative studies were found, the SLRs described in Section 3.1 are assumed to be the source of the studies used in the ITCs. This is suggested by the studies in Table 3.32 above all being part of the 'included' lists across the 5 SLRs. The company have been asked to confirm this. The company confirmed that, *"evidence source for the ITC and MAIC were obtained from the SLRs conducted for each of the tumour site of interest in this appraisal. The response to A44 outlines which studies were selected for the ITC from the studies identified in the SLR along with the rationale".*
- Although all the studies in Table 3.32 are derived from the SLRs, it is not clear if there were additional studies yielded by the SLRs that might also have been relevant in terms of the comparators listed in Table 3.32. For example, it is unclear why Hirai 2004 and Homesley 2008 (to list just two examples), were not included in the ITC/MAIC for endometrial cancer. Both studies evaluated paclitaxel which was the comparator listed for endometrial cancer in Table 3.32. The company have been asked to explain the rationale for this apparent anomaly. The company stated that *"of the thirteen comparator studies, only KEYNOTE-775 includes outcome data for participants with dMMR tumours. The remainder of the studies were conducted in the unselected population and therefore were not selected as the efficacy source for the relevant comparator given the lack of outcomes specifically reported for MSI-H/dMMR patients"*. The EAG thinks this is a reasonable response.
- It is important to be sure that the comparators outlined in Table 3.32 concur with the decision problem. There appears to be correlation for colorectal, gastric and biliary cancer, but not for endometrial or small intestine cancer. For endometrial cancer, the decision problem includes carboplatin as a comparator, but this is absent from Table 3.32. For small intestine cancer, the decision problem includes FOLFORI/FOLFOX but Nab-paclitaxel is used in Table 3.32 instead. These two departures from the decision problem mean that the ITC/MAIC analyses for endometrial and small intestine cancer would not be relevant to the decision problem. The company has been asked to explain these departures. The company stated that, "*Exclusions of comparators stated in the NICE scope are justified based on clinical opinion but also consensus from previous appraisals in the relevant tumour site.*

Endometrial

Based on clinical expert consultation and published guidelines, standard of care is chemotherapy such as paclitaxel, doxorubicin and carboplatin. The chemotherapy arm (physician's choice of paclitaxel or doxorubicin) from KEYNOTE-775 was used to inform efficacy for these chemotherapies as there was clinical consensus that efficacy will not vary significantly between these. This is also supported by ongoing appraisal ID3811 that also listed "Chemotherapy (such as paclitaxel, carboplatin, doxorubicin)" as a comparator but there was consensus that the TPC arm of KEYNOTE-775 broadly reflects the efficacy for these chemotherapies. The support for KEYNOTE-775 as reflective of these is also seen in TA779 where this was the preferred source of data for this specific comparator grouping. Hormone therapy is only used with palliative intent if all other treatment options are exhausted, or patients cannot tolerate further lines of chemotherapy. This positioning was also supported by consensus in the ongoing appraisal ID3811 and no comparison was made with hormone therapies (despite it being in the NICE scope).

Small intestine cancer

With regard to small intestine cancer, clinical experts identified FOLFOX/FOLFIRI as the treatment of choice but did not expect MSD to find any published evidence on efficacy. This was confirmed in the systematic literature review which only identified evidence for nab-paclitaxel, which is used in the cost-effectiveness analysis (see response to question e below). Clinical consensus was that this would be a reasonable proxy, given the lack of other efficacy data."

The EAG think that these responses provide reasonable justification for the departures from the decision problem.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

As the pembrolizumab data were derived from single-arm studies, ITC methods were used to estimate the effects of pembrolizumab relative to relevant comparators. The only outcomes estimated were OS and PFS, which were evaluated for all tumour subgroups.

ITCs without adjustment for confounders and effect modifiers were conducted based on Cox proportional hazards models for all comparators. Where the effective sample size (ESS) was deemed sufficient, and sufficient data were available, a matching-adjusted indirect comparison (MAIC) was conducted in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18. Unadjusted ITC methods were used for the majority of evidence, whilst adjusted methods (MAIC) were used for endometrial cancer data. Table 3.37 above summarises the methods used in the different tumour subgroups.

Choice of the comparators for the ITCs was made on a tumour site by tumour site basis, based on suitability. Except for paclitaxel in gastric cancer and paclitaxel/doxorubicin in endometrial, there were no published data available for comparators in MSI-H/dMMR-specific populations. The company stated that this is likely to result in conservative estimates of relative efficacy, stating that evidence suggests that MSI-H/dMMR patients may have worse outcomes compared to patients with MSS or proficient mismatch repair (pMMR) disease. The final list of comparators used for the ITC for each tumour site was described by the company as reflecting current clinical guidelines, clinical expert validation or refences in previous NICE appraisals (Table 3.37). The list of comparators includes a pooled group of three regimens: FOLFIRI (folinic acid, fluorouracil and irinotecan), FOLFOX4 and FOLFOX6 (two different regimens of folinic acid, fluorouracil and oxaliplatin). This group is referred to as pooled FOLFOX/FOLFIRI. The pooled comparator was chosen for the colorectal tumour site to

maximize the relevant data. Grouping of different comparators was permitted by the company because UK clinical experts confirmed that they would not expect efficacy or safety outcomes to vary between individual regimens within each respective group.

EAG comment:

- Although references were cited to show the effect of MSI-H/dMMR on metastatic colorectal cancer (mCRC), endometrial cancer and advanced gastric cancer, no references were given for small intestine or biliary cancer, making this claim impossible to verify.
- The comparators chosen do not fully reflect the NICE scope, nor the company's decision problem. Any ITC may therefore fail to generate measures of effect that reflect the NICE remit.

3.4.1 Unadjusted ITCs

For each comparator, survival outcomes were extracted from the relevant publications and pseudo-IPD were generated by digitization, using methods described by Guyot 2012.[27] To provide a meaningful comparison where there was more than one relevant study, pooled KM curves were derived to synthesize information across the studies. If only one study was used for comparison against pembrolizumab, KM curves were presented without pooling.

A summary of the outcomes of the unadjusted ITC, in the form of OS and PFS HRs, is presented by comparator and by tumour site in Table 3.46. Further details of methods and results (baseline characteristics, summary statistics, K-M curves and) were presented in Appendix P of the CS.[28]

Table 3.46: OS and PFS HRs for pembrolizumab versus comparator therapies, by tumour site

Tumour site	Comparator	HR versus comparator (95% CI)	
		OS	PFS
CRC	TAS-102	0.26 (0.18; 0.38)	0.34 (0.25; 0.46)
	Pooled FOLFOX/FOLFIRI	0.30 (0.23; 0.39)	0.54 (0.43; 0.69)
Endometrial	Chemotherapy (physician's choice of paclitaxel or doxorubicin)	0.29 (0.18; 0.48)	0.39 (0.26; 0.60)
Gastric	FOLFIRI	0.40 (0.23; 0.71)	0.41 (0.24; 0.70)
	Paclitaxel	0.52 (0.25; 1.09)	0.73 (0.36; 1.51)
Small intestine	Nab-paclitaxel	0.18 (0.07; 0.45)	0.22 (0.09; 0.52)
Cholangiocarcinoma	mFOLFOX	0.30 (0.16; 0.58)	0.50 (0.27; 0.92)
	mFOLFIRI	0.27 (0.14; 0.54)	0.36 (0.18;0.71)

Based on Table 30 of the CS[2]
CI = confidence interval; CS = company submission; CRC = colorectal cancer; HR = hazard ratio; mFOLFIRI = modified folinic acid, fluorouracil, irinotecan; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; OS = overall survival; PFS = progression-free survival; TAS 102 = tipiracil hydrochloride

Assessment of the log-cumulative hazards plots for each comparator indicated that the proportional hazards assumption was violated. This was explained by the company as being due to pembrolizumab being associated with long-term survival benefits and an established "functionally cured" group by around 5 years irrespective of tumour site (as validated by clinical experts), which is different to the survival patterns of comparators. Due to the small sample size available within each tumour site, it was not feasible to explore methods to generate time-varying hazard ratios (HRs) that do not rely on the proportional hazards assumption. For this reason, the resulting HR estimates were considered inappropriate and were not investigated further within the cost effectiveness analysis.

Instead, separate parametric survival distributions were fitted to the available pseudo-individual participant data (IPD) for each comparator and are used within the economic analysis. The number of

patients at risk over time alongside the digitised KM curve from the published literature are used to derive pseudo- individual participant level data using the method developed by Guyot 2012.[27] This approach of fitting separate parametric survival distributions does not require the proportional hazards assumption to hold.

EAG comment:

- The ITC uses comparator trials that are not in the high microsatellite instability or mismatch repair deficiency population. The company stated that the estimates from such an ITC would produce conservative estimates of relative efficacy because "…*evidence suggests that MSI-H/dMMR patients may have worse outcomes compared to patients with MSS or pMMR disease*." (p. 70). The company have been asked to provide references to back this up. The company reiterated studies cited in the CS that suggested that MSI-H status may worsen prognosis, and referred to discussion at the ad-board, where "*there was a consensus that MSI-H/dMMR status is potentially a negative prognostic factor*". However, to assume conservative estimates of relative efficacy, it is not enough for MSI-H to confer a negative prognosis, as this does not factor in the interaction with treatment effectiveness. It is quite possible for MSI-H to confer a worse prognosis, whilst also conferring a *better* response from a treatment. To improve comparability, the EAG requested a comparison using pembrolizumab trials more like the comparator trials, i.e. not using the MSI-H/dMMR patients data from the KEYNOTE-158 and -164 trials. In response the company stated: "*there was more consensus that MSI-H/dMMR status is a treatment effect modifier for immunotherapies (i.e. they will be more efficacious in MSI-H/dMMR patients other things being equal).*" However, no evidence was provided to support this assertion and one of the comparators in the NICE scope, but omitted by the company is also immunotherapy i.e., nivolumab + ipilimumab.
  Therefore, the mismatch in MSI-H/dMMR status between pembrolizumab trial population and comparator trial populations has been identified as a key issue.
- An examination of the survival curves, log cumulative hazard and Schoenfeld residual plots seems to indicate that a rejection of the proportional hazards assumption is reasonable.
- Comparisons of baseline characteristics between pembrolizumab and the comparator trials reveals differences that might be regarded as substantial (see Appendix P).[28] This might therefore also imply biases in addition to the effect of MSI-H/dMMR status. Indeed, some characteristics are identified as treatment effect modifiers (see Section 3.4.2 below). This would therefore suggest that, notwithstanding the lack of randomised trial evidence, any naïve ITC is subject a high risk of bias, the direction of which is difficult to predict.

3.4.2 MAICs

If a sufficiently ESS was obtained after matching, an ITC with adjustment for confounders and effect modifiers was performed using an MAIC. MAICs were only possible in one case: physician's choice of paclitaxel or doxorubicin in endometrial cancer.

3.4.2.1 KEYNOTE-158 MAIC methods

The following baseline characteristics, identified as potential effect modifiers and/or key prognostic factors based on clinical expertise, were selected as matching variables for both OS and PFS endpoints:

- Age (median)
- Race (White, Black, Asian, other)
- Eastern Cooperative Oncology Group (ECOG) (0 vs 1)
- Number of prior lines of therapy (1 vs ≥2)
- Histology status (endometrioid carcinoma, others)

3.4.2.2 KEYNOTE-158 MAIC results

Selected key baseline characteristics are summarised in Table 3.47 for the comparison between pembrolizumab and physician's choice of paclitaxel or doxorubicin. For pembrolizumab (KN158) versus physician's choice (KN775), the ESS after matching is 34.87, which is a reduction of 58% of the original sample size of 83.

Table 3.47: Baseline characteristics

	Physician's choice (N[c]=65)	Before matching (N[b]=83)	After matching (N=34.87[d])
Age			
Median	63.0	64.0	62.0
ECOG performance status (%)			
0	52.3	45.8	52.3
1	47.7	54.2	47.7
Race (%)			
White	53.8	84.3	53.8
Black	7.7	3.6	7.7
Asian	18.5	6.0	18.5
Other	20.0	6.0	20.0
Prior lines of therapy (%)			
1	78.5	53.0	78.5
≥2	21.5	47.0	21.5
Histology (%)			
Endometrioid carcinoma	86.2	65.1	86.2
Other	13.8	34.9	13.8

Based on Table 31 of the CS[2]
a: Database Cut-off date: 15OCT2021
b: Number of participants: Based on KEYNOTE 158, All-Participants-as-Treated population for efficacy analysis, Cohort K, MSI-H with Endometrial Carcinoma, at least one line of prior therapy
c: Number of participants: Based on Makker 2022
d: Effective sample size computed as the square of the summed weights divided by the sum of the squared weights; Weighted according to matched baseline characteristics of selected comparators
Selected comparators: treatment of physician's choice (TPC) based on Makker 2022
CS = company submission; ECOG = Eastern Cooperative Oncology Group

3.4.2.2.1 Overall survival

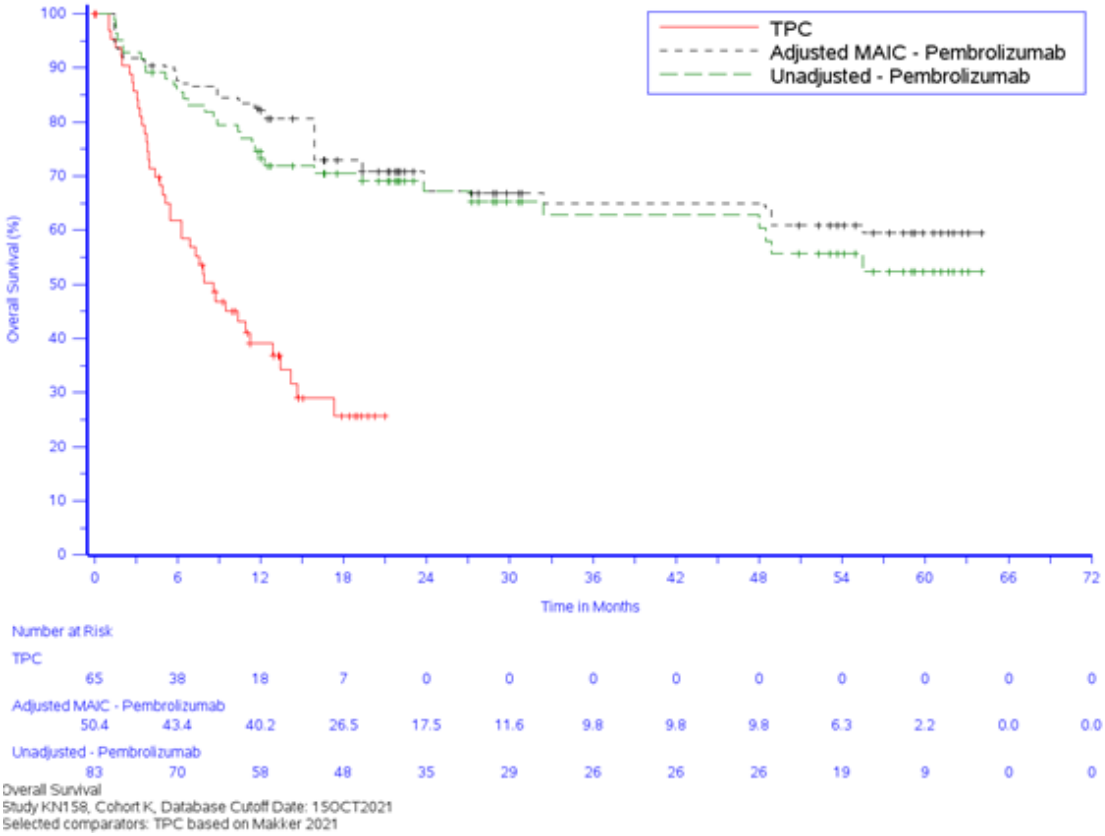
The results of the OS analysis for the ASaT population are presented in Table 3.48, and the corresponding KM curve is presented in Figure 3.9. The outcomes both before and after matching show a statistically significant favourable HR (i.e., <1) towards pembrolizumab.

Table 3.48: Analysis of overall survival

Study: KEYNOTE 158[a]	Pembrolizumab			Physician's choice			Pembrolizumab vs physician's choice	
	N[b]	Participants with event, n (%)	Median time[c] in months [95%-CI]	N[d]	Participants with event, n (%)	Median time[c] in months [95%-CI]	Hazard ratio [95%-CI][e]	P-value[e,f]
Before matching	83	32 (38.6)	Not reached [48.0; -]	65	42 (64.6)	8.6 [5.5; 12.9]	0.29 (0.17, 0.48)	<0.001
After matching[g]	50.4[h]	16 (31.7)	Not reached [23.8; -]	65	42 (64.6)	8.6 [5.5; 12.9]	0.23 (0.12, 0.48)	<0.001

Based on Table 32 of the CS[2]
a: Database cut-off date: 15OCT2021
b: Number of participants: Based on KEYNOTE 158, All-Participants-as-Treated population for efficacy analysis, Cohort K, MSI-H with Endometrial Carcinoma, at least one line of prior therapy
c: From product-limit (Kaplan–Meier) method for censored data
d: Number of participants: Based on Makker 2022
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Matching was done on the following covariates: Age (Median), ECOG Status, Race, Prior Lines of Therapy and Histology Status
h: Sample size after matching computed as the sum of the weights
Selected comparators: TPC based on Makker 2022.
CI = confidence interval; CS = company submission; MSI-H = microsatellite instability-high; TPC = treatment of physician's choice (doxorubicin or paclitaxel)

Figure 3.11: KM curve for overall survival



Based on Figure 12 of the CS[2]

CS = company submission; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; TPC = treatment of physicians' choice (doxorubicin or paclitaxel)

3.4.2.2.2 Progression-free survival

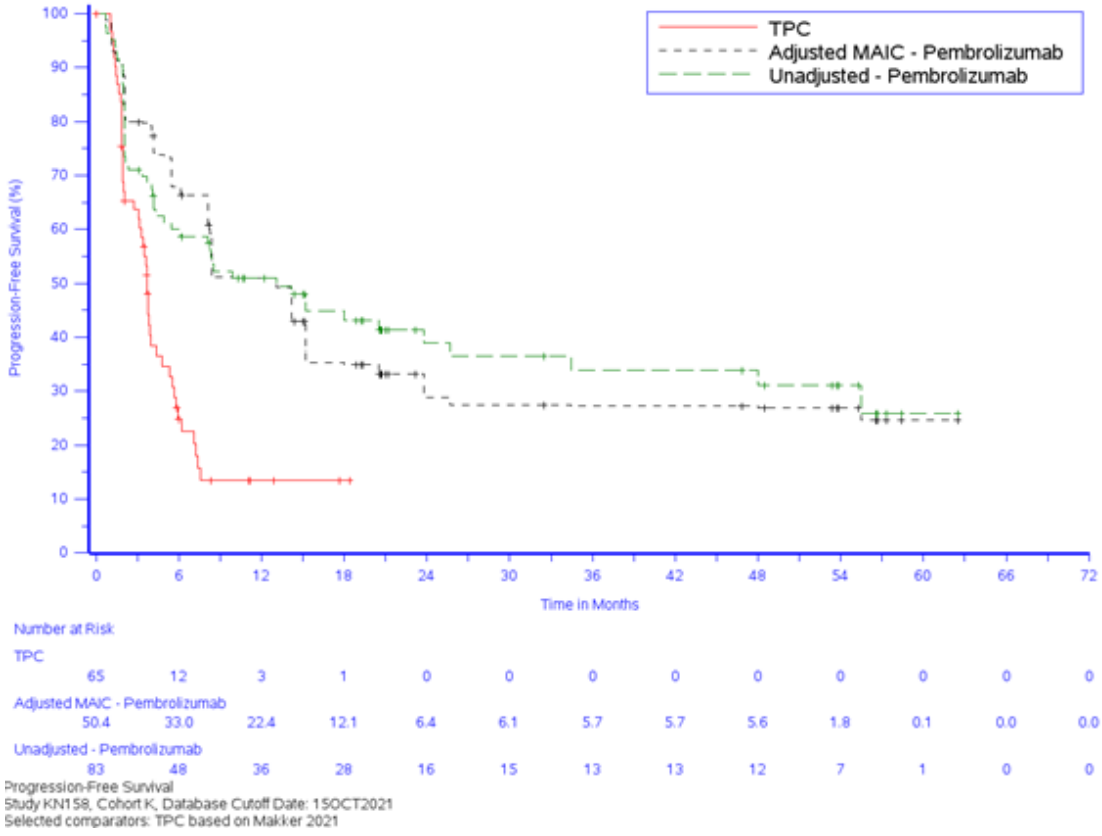
The results of the PFS analysis for the ASaT population are presented in Table 3.49, and the corresponding KM curves are presented in Figure 3.12. As for OS, the outcomes both before and after matching show a statistically significant favourable HR (i.e., <1) towards pembrolizumab.

Table 3.49: Analysis of progression-free survival

Study: KEYNOTE 158[a]	Pembrolizumab			Physician's choice			Pembrolizumab vs physician's choice	
	N[b]	Participants with event, n (%)	Median time[c] in months [95%-CI]	N[d]	Participants with event, n (%)	Median time[c] in months [95%-CI]	Hazard ratio [95%-CI][e]	P-value[e,f]
Before matching	83	51 (61.4)	13.1 [4.9; 25.7]	65	48 (73.8)	3.7 [3.1; 4.4]	0.40 (0.26, 0.62)	< 0.001
After matching[g]	50.4[h]	32 (63.5)	13.1 [5.5; 20.5]	65	48 (73.8)	3.7 [3.1; 4.4]	0.35 (0.20, 0.59)	< 0.001

Based on Table 33 of the CS[2]
a: Database Cut-off date: 15OCT2021
b: Number of participants: Based on KEYNOTE 158, All-Participants-as-Treated population for efficacy analysis, Cohort K, MSI-H with Endometrial Carcinoma, at least one line of prior therapy
c: From product-limit (Kaplan–Meier) method for censored data
d: Number of participants: Based on Makker 2022
e: Based on Cox regression model with treatment as a covariate
f: Two-sided p-value using Wald test (Score test in case of zero event in one treatment group)
g: Matching was done on the following covariates: Age (Median), ECOG Status, Race, Prior Lines of Therapy and Histology Status
h: Sample size after matching computed as the sum of the weights
Selected comparators: TPC based on Makker 2022
CI = confidence interval; CS = company submission; MSI-H = microsatellite instability-high; TPC = treatment of physician's choice (doxorubicin or paclitaxel)

Figure 3.12: KM curve for progression-free survival



Based on Figure 13 of the CS[2]

CS = company submission; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; TPC = treatment of physicians' choice (doxorubicin or paclitaxel)

EAG comment:

- The company has been asked to give a full explanation (further to the reasons already given in the CS[2]) why a MAIC was used for one population and not the others. The company has been asked to conduct a MAIC for all cancer subgroups. The company responded by stating that *"the decision to conduct MAICs over ITCs was based on a balance between impact on effective sample size; likely impact of treatment effect when adjusting vs. not adjusting; and availability of data to allow weighting on chosen variables. The more variables for weighting and related number of covariates can mean a MAIC cannot be run or that the effective sample size after weighting is very small. The sample sizes within the gastric tumour type (n=51), small intestine (n=27), and cholangiocarcinoma (n=20) are likely too small to support MAIC analyses. To illustrate, the weighting based on 5 variables listed in B.2.9 reduced the sample size by 58% in the endometrial MAIC (vs. TPC). In addition, the impact was relatively minimal in endometrial, and this may be because the TPC source is from a MSI-H/dMMR selected source. The relevant five variables for weighting were not always available; for example in small intestine Overman et al. 2018 did not contain adequate histology information or line status in the relevant form; in gastric (FOLFIRI comparison) Moehler et al. 2016 did not report performance status by ECOG. In a similar way unadjusted ITC methods were chosen for CRC because many of the sources used for KM pooling (i.e. chosen to reflect comparator efficacy) did not have the relevant weighting variables. For example, Moore et al. 2016, a source for FOLFIRI efficacy, did not report an adequate breakdown of previous lines of treatment."* The EAG is satisfied with this response.

- For endometrial cancer, it appears that the company's own trial (KN775) was used. The company has been asked to explain why population adjustment was used instead of an individual patient data method of adjustment, as described in NICE TSD 17. Where IPD is available for the comparator, the company has been asked to conduct an analysis, providing a full assessment of validity such as the QuEENS checklist, following the recommendations of TSD 17.The company responded by stating that, "*The KEYNOTE-775 trial was conducted as part of an alliance with both Merck and Eisai as the sponsors and data owners. The KEYNOTE-158 submission is outside of this alliance and MSD does not have the authority to use individual patient data from the KEYNOTE-775 trial to support submissions outside of the alliance. Therefore, only publicly available data from KEYNOTE-775 were digitized and used to support the KEYNOTE-158 submission.*" The EAG is satisfied with this response.

3.4.3 Limitations raised by the company

The MAIC follows the recommendations in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18, which states: *"for an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables"*.[29] Where possible, differences in patient characteristics were adjusted for to reduce bias; however, it was not possible to match for all characteristics given the substantial heterogeneity between KEYNOTE-158 and comparator studies. The key modifier was MSI-H/dMMR status, which could not be adjusted for in any potential MAICs involving MSI-unselected sources given the lack of baseline reporting. For the MAIC conducted versus treatment of physician's choice (TPC) in endometrial cancer, MSI-H/dMMR status could not bias results given that patients were selected based on status.

Unanchored MAICs will also always be subject to unknown amounts of residual bias due to unobserved prognostic variables and effect modifiers. Furthermore, it was not possible to adjust comparator studies for the potential impact of MSI-H/dMMR status. This, combined with the small population sizes for some tumour sites in KEYNOTE-158 and the lack of reported data for comparators, meant that MAICs were infeasible in most cases. However, failing to adjust for MSI-H/dMMR is likely to result in conservative estimates of relative efficacy, as evidence suggests that patients with MSI-H/dMMR disease may have worse outcomes compared to patients with microsatellite stable (MSS) or pMMR disease, and should be taken into consideration when interpreting the modelled comparator outcomes. Consulted clinicians agreed that MSI-H/dMMR status is a potential negative prognostic variable, but emphasized that MSI-H/dMMR status is at least a treatment effect modifier for immunotherapies (i.e., they will be more efficacious in MSI-H/dMMR patients, other things being equal).

The company therefore concluded that *"given the limitations and potential bias of the unadjusted ITCs and unanchored MAICs, neither were used further in the economic analyses. Therefore, parametric survival distributions were fitted to the comparator pseudo-IPD with the most clinically plausible extrapolation chosen for use in the base-case. While the company acknowledged that this method is not ideal, the company considered it the most reasonable in light of the evidence and potential bias introduced from other tested methods"* (p. 80).

EAG comment:

- The company states that the economic analysis is based upon *"parametric survival distributions … fitted to the comparator pseudo-IPD with the most clinically plausible extrapolation chosen for use in the base case"*. This description is highly ambiguous and unclear. The company has been asked to explain the criteria for the 'most clinically plausible extrapolation'. The company failed to respond to this question.

- It is difficult to find the source of the comparator data used for the parametric survival distributions approach in the company documents. The company has been asked to highlight the location of these results, or, if not, to make them available. The company responded by stating that, "*It's not clear what is meant here or if this refers to the parametric BHM base-case or standard parametric models. Appendix J includes "raw" hazard plots overlayed with hazards from parametric models. If this question refers to landmark proportions, these are automatically calculated from the model at 1,2, 3, 10 and 15 years when new parametric models are selected (e.g., BHM, standard PSM, BHM piecewise for PFS and specific functions) and deterministic model re-run (see "Summary KM" and "summary outcomes" tables in PFS and OS sheets for this).*" It appears the company were unaware that the EAG were referring to the location of the comparator clinical effectiveness results that directly informed the economic analysis. The company's failure to answer this question satisfactorily means that the lack of clarity around this issue remains.
- As an alternative to using 'parametric survival distributions … fitted to the comparator pseudo-IPD with the most clinically plausible extrapolation chosen for use in the base case', the company considered using 'non-responder analyses'. The company decided not to use this method, which seemed reasonable in the EAG's view. A non-responder analysis has the advantage of comparability of responders and non-responders in terms of MSI-H/dMMR status, but, given difference in response, difference in other prognostic characteristics is probable. Such analyses also rely on the assumption of similarity of outcome between non-responders and the comparator. Therefore, the EAG agrees with the company in being very sceptical of non-responder analyses as an alternative.
- In conclusion, it seems that all methods of comparing survival have serious limitations: the ITC relies on proportional hazards and there is no adjustment for confounding, any MAIC is limited by lack of data by which there could be adjustment for confounding, and the non-responder-based analysis relies on a strong assumption of comparability between non-responder and comparator outcomes. The method chosen as the base case does have the advantage of no reliance on proportional hazards, but there is still no adjustment for confounding. Therefore, there remains a high risk of bias in the comparative efficacy for pembrolizumab for all types of cancer.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None

3.6 Conclusions of the clinical effectiveness section

Five solid cancer populations of the MSI-H/dMMR sub-type are included: colorectal, gastric, biliary, small intestine and endometrial. Pembrolizumab is provided as a second line (or later) therapy, and compared to second line (or later) TAS-102 [CRC], pooled FOLFOX/FOLFIRI [CRC], physician's choice of paclitaxel or doxorubicin [endometrial], FOLFIRI [gastric], paclitaxel [gastric], and-paclitaxel [small intestine], mFOLFOX [biliary] or mFOLFIRI [biliary]. The scope of comparators is a key issue, as the NICE scope had recommended established clinical management, which has been excluded, as well as several specific therapies, some of which have been excluded. The company has not been able to justify these exclusions satisfactorily, and there is therefore a risk that these exclusions may influence the final clinical effectiveness and cost effectiveness of pembrolizumab.

The trial data from pembrolizumab are the single-arm studies KN158 [subgrouped into endometrial, gastric, biliary, and small intestine populations] and KN164 [single CRC population]. Therefore, ITC and MAIC analyses were undertaken to allow the single-arm pembrolizumab trials to be compared to the company's chosen comparators. These show that both OS and PFS are significantly extended by pembrolizumab compared to almost all the comparators across almost all the tumour subgroups (except compared to paclitaxel for gastric cancer). These effects (except those compared to paclitaxel for gastric

cancer) are statistically significant, and show a magnitude of effect that is likely to be clinically important.

The pembrolizumab trials are restricted to the MSI-H/dMMR solid cancer sub-type, but have been compared in the ITC/MAIC analyses with comparators that have not been restricted to this sub-type. This mismatch may be an effect modifier. The company provided evidence that suggested MSI-H/dMMR status may worsen prognosis. This implies that the mismatch is a conservative effect modifier, which may reduce rather than enhance apparent pembrolizumab effectiveness. However, the company also cites clinical opinion suggesting that MSI-H/dMMR status may improve the effectiveness of immunotherapy treatment. This additional effect may increase uncertainty of the magnitude and direction of any effect modification.

For colorectal and gastric cancer, and to a lesser extent small intestine cancer, the EAG notes large differences in ethnicity between the trials and the UK data provided by the company. The UK data is not specifically in people with MSI-H/dMMR, and the EAG recognises that it is possible that the ethnic proportions in a more relevant UK subgroup with MSI-H/dMMR status might be more closely aligned with the trial data (which is in an MSI-H/dMMR population). However, given evidence that ethnicity is not strongly linked to MSI-H/dMMR status (Ashktorab, 2016),[26] it is unlikely that the ethnic make-up of a UK MSI-H/dMMR subgroup would be appreciably different to the ethnic make-up of the UK data presented by the company. Given that the UK data may reflect the ethnic proportions of the specific UK target population, there are possible discrepancies between the trial data and the UK target population.

Aggregation of data for the four tumour sites were combined for appraisal of AEs. It is possible that an aggregated result could obscure high levels of adverse events in a single tumour site.

Having presented the ITC and MAIC evidence, with its limitations as described above, the company concludes that the ITC and MAIC evidence is not fit for purpose for the economic analysis, and that the health economic strategy will therefore be based upon the following approach: "*parametric survival distributions were fitted to the comparator pseudo-IPD with the most clinically plausible extrapolation chosen for use in the base case*". In conclusion, it seems that all methods of comparing survival have serious limitations: the ITC relies on proportional hazards and there is no adjustment for confounding, any MAIC is limited by lack of data by which there could be adjustment for confounding, and the non-responder-based analysis relies on a strong assumption of comparability between non-responder and comparator outcomes. The method chosen as the base case does have the advantage of no reliance on proportional hazards, but there is still no adjustment for confounding. Therefore, there remains a high risk of bias in the comparative efficacy for pembrolizumab for all types of cancer.

4. COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search Section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.[30] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[4, 5] The EAG has presented only the major limitations of each search strategy in the report.

The company provided five separate documents within appendix G containing separate searches for papers relevant to economic modelling, cost & resource use and utilities for the five conditions of interest. Searches were performed between June and July 2021.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations (as reported in CS)

Resources	Economic modelling	Cost and resource use	Utility
Endometrial cancer			
Embase (Embase.com)	DR: 2011-Current SD: 14.06.21	DR: 2011-Current SD: 15.06.21	DR: Inception-Current SD: 15.06.21
MEDLINE In Process (PubMed)	DR: Inception-Current SD: 14.06.21	DR: Inception-Current SD: 15.06.21	DR: Inception-Current SD: 15.06.21
Econlit (EBSCO)	DR: Inception-Current SD: 14.06.21	DR: Inception-Current SD: 15.06.21	DR: Inception-Current SD: 15.06.21
HTAD and NHS EED (CRD)	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 14.06.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 15.06.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 15.06.21
Small intestine cancer			
Embase (Embase.com)	DR: 2011-Current SD: 17.06.21	DR: 2011-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21
MEDLINE In Process (PubMed)	DR: Inception-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21
Econlit (EBSCO)	DR: Inception-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21
HTAD and NHS EED (CRD)	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 17.06.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 17.06.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 17.06.21
Gastric cancer			
Embase (Embase.com)	DR: 2011-Current SD: 17.06.21	DR: 2011-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21

Resources	Economic modelling	Cost and resource use	Utility
MEDLINE In Process (PubMed)	DR: Inception-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21
Econlit (EBSCO)	DR: Inception-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21	DR: Inception-Current SD: 17.06.21
HTAD and NHS EED (CRD)	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 17.06.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 17.06.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 17.06.21
Biliary cancer			
Embase (Embase.com)	DR: 2011-Current SD: 09.07.21	DR: 2011-Current SD: 09.07.21	DR: Inception-Current SD: 09.07.21
MEDLINE In Process (PubMed)	DR: Inception-Current SD: 09.07.21	DR: Inception-Current SD: 09.07.21	DR: Inception-Current SD: 09.07.21
Econlit (EBSCO)	DR: Inception-Current SD: 09.07.21	DR: Inception-Current SD: 09.07.21	DR: Inception-Current SD: 09.07.21
HTAD and NHS EED (CRD)	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 09.07.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 09.07.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 09.07.21
Colorectal cancer			
Embase (Embase.com)	DR: 2011-Current SD: 13.07.21	DR: 2011-Current SD: 12.07.21	DR: Inception-Current SD: 13.07.21
MEDLINE In Process (PubMed)	DR: Inception-Current SD: 13.07.21	DR: Inception-Current SD: 13.07.21	DR: Inception-Current SD: 13.07.21
Econlit (EBSCO)	DR: Inception-Current SD: 13.07.21	DR: Inception-Current SD: 13.07.21	DR: Inception-Current SD: 13.07.21
HTAD and NHS EED (CRD)	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 13.07.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 13.07.21	HTAD DR: Inception-2018.03.31 NHS EED DR: Inception-2015.03.31 SD: 13.07.21

CRD = Centre for Reviews and Dissemination; CS = company submission; DR= date range, EED = Economic Evaluation Database: HTAD = Health Technology Assessment Database, NHS = National Health Service, SD =search date

EAG comment:

General

- The EAG noted that the company's economic searches reported a joint search of MEDLINE and Embase via Ovid.com. The company confirmed Embase was searched on the understanding that it contains all MEDLINE content. Whilst the company stated that Embase's mapping of MEDLINE records to Embase's own Emtree terms removed the necessity of searching MEDLINE as a separate search. Whilst Embase.com should automatically identify and search for equivalent MEDLINE subject heading terms (MeSH), it is unclear if this is the case for all potentially useful MeSH terms. A separate search also allows the searches to fully utilise the power of database specific study design filters developed to make the most of an individual database's subject headings, for these reasons the EAG considers it preferable to conduct a separate MEDLINE search.
- The CS reported that MEDLINE In-Process was searched using PubMed for all of the economics searches. However, this is inaccurate, as the search limit used in PubMed identifies recently added

records, not in-process records: (publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint). The correct subset to use is 'inprocess[sb]'.[31] Omitting this subset from the limits used resulted in MEDLINE In-process records being excluded from the company's PubMed searches.

- The EAG noted that all economics searches reported for all topics had search dates of June 2021 and queried if any updates were run. The company responded *that "Given the scale and resources required to complete the original SLR and limited relevant studies identified, a pragmatic targeted literature review was conducted instead which searched for economic evaluations within the target population of interest. This search was conducted on 12 August 2022 with no relevant economic evaluations identified that were consistent with the target population."*[3] Details of a targeted literature review were reported in section 2.3 of appendix G, but as no search dates were reported the EAG is unable to verify if these are the correct searches.

Colorectal Cancer economics searches

- The company confirmed the presence of a reporting error in the final line combination (line #15) for each of the Centre for Reviews and Dissemination (CRD) searches reported for colorectal cancer (Section 2.1.1). The final line should read "(#14) IN NHSEED, HTA" rather than "(#23) IN NHSEED, HTA". Again, the EAG would refer to the best practice recommendations cited above to report strategies as run rather than reformatting into tables and risking the inclusion of reporting errors.

Gastric Cancer economics searches

- The company confirmed the presence of a reporting error in line #7 of each of the Embase strategies (see Table 2 in Section 2.1.1, Table 6 in Section 2.1.2, and Table 10 in Section 2.1.3) rather than "#4 OR #5 OR #6", this should have read "#4 AND #5 AND #6".

Small Intestine cancer economics searches

- There appeared to be an error in the reporting of hits per line in the Embase strategy in Table 2 in Section 2.1.1. The company confirmed that this was a reporting error and should read as follows: 14. #13 AND [2011-2021]/py 249

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Adults (≥ 18 years) with advanced/metastatic CRC, pancreatic cancer, cholangiocarcinoma and gall bladder cancer, small intestine cancer and endometrial cancer with MSI-H/dMMR tumour and who are receiving second-line or later therapy Additionally, studies in adult patients suffering from any of the above six advanced/metastatic indications, receiving second-line or later therapy and reporting data for the broader population (not MSI-high/dMMR tumour specifically) were also included in the review	Healthy volunteers Patient population other than specified in the inclusion
Intervention	All pharmacological interventions	None

	Inclusion criteria	Exclusion criteria
Comparator	No restrictions	None
Outcomes(s)	Model summary (type of model, model structure, perspective, time horizon, cycle length, cost year, discounting, etc.) Sources of clinical, cost, resource use and utility inputs Model results (QALYs/incremental QALY, DALYs/incremental DALY, LYs/incremental Lys, ICER) Any other measure of effectiveness reported together with costs Health states Key model drivers Sensitivity analysis (including variability reported around the parameters) and model assumptions	Studies not reporting model outputs Studies reporting clinical data only
Study design	Cost consequence Cost–minimisation Cost effectiveness Cost–utility Cost–benefit Budget impact Systematic reviews[a]	Letters, comments, and editorials Clinical studies reporting efficacy and safety data Letters, comments, and editorials Clinical studies reporting efficacy and safety data

Based on Table 1 of Appendix G of the CS[30]

[a] Systematic reviews were included for bibliography searches

CRC = colorectal cancer; CS = company submission; DALY = disability-adjusted life year; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; ICER = incremental cost-effectiveness ratio; LY = life year; MSI-H = microsatellite instability-high; QALY = quality-adjusted life year

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationales for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.1.3 Conclusions of the cost effectiveness review

The CS Appendix G provides an overview of the included cost effectiveness, utility and resource use and costs studies, but no specific conclusion was formulated. Further, the EAG did not find an overview of studies that were referenced in the CS.

EAG comment: Eligibility criteria were suitable for the SLR performed. The CS[2] and response to clarification[3] provided sufficient details for the EAG to appraise the literature searches provided in five separate documents within Appendix G containing separate searches for papers relevant to economic modelling, cost and resource use and utilities for the five conditions of interest. Searches were performed between June and July 2021. Searches were transparent and reproducible. Whilst the strategies provided appeared appropriate, the EAG would have preferred to see a separate search of the MEDLINE database.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with reference case
Perspective on costs	NHS and PSS	Consistent with reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Consistent with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Consistent with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Consistent with reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with 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	Consistent with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with reference case

EAG = Evidence Assessment Group; EQ-5D = EuroQol 5D quality of life instrument; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year; UK = United Kingdom

4.2.2 Model structure

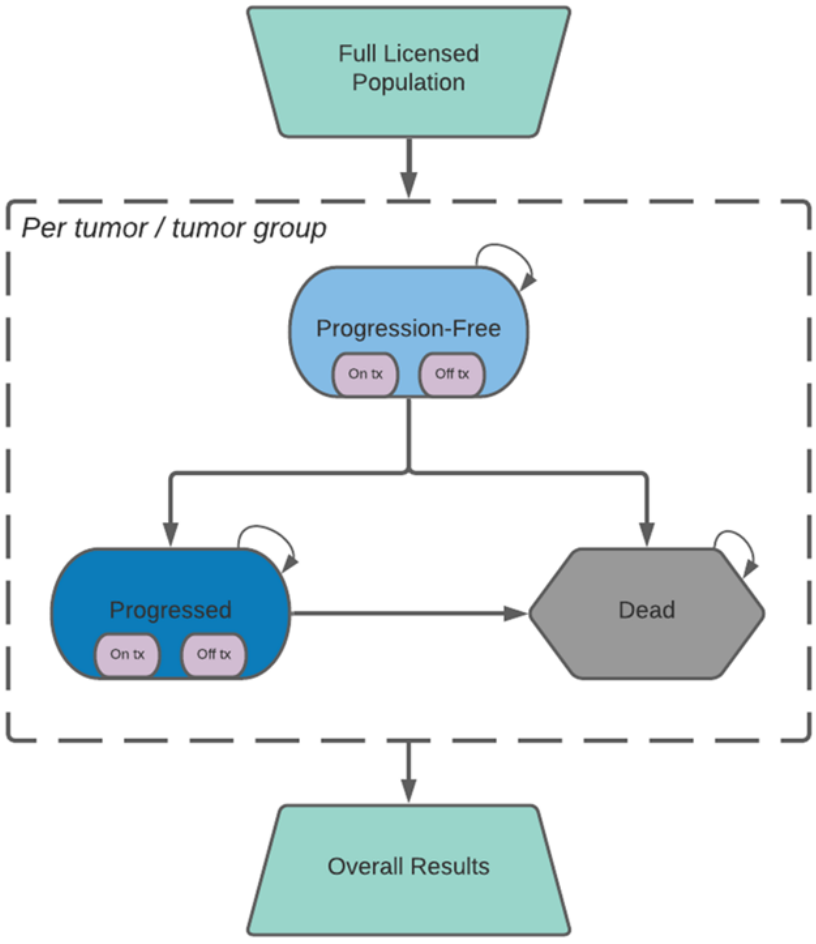
The company suggested no previous economic evaluations have aligned with the decision problem in question. As such, a de novo multi-cohort partitioned survival model (PSM) was developed in Microsoft Excel, encompassing three mutually exclusive health states: a PF state, a progressed disease state, and death (Figure 4.1). To capture drug administration and acquisition costs, alive states were further separated into on- and off-treatment. The same multi-cohort structure was used to model each tumour site separately and then aggregate to generate outcomes across all tumour sites (weighted by tumour site prevalence). According to the CS, the PSM model structure was chosen to reflect the clinical

pathway of disease, and for its simplicity and flexibility to allow for survival to be extrapolated using various methods, for the incorporation of relative efficacy using different methods, and to simultaneously consider several indications without overcomplication.

The allocation of patients into each health state was derived from independently modelled time to treatment discontinuation (TTD), PFS, and OS curves. The area under the curve approach was used to calculate health state occupancy over time. All patients entered the model in the PF state and were treated with pembrolizumab or standard of care (SoC) (a basket of comparators). Patients in the PF state remained in that state, progressed, or died. Patients in the progressive disease (PD) state remained alive with PD or died, with dead being the absorbing state.

A lifetime time horizon of 40 years with a weekly cycle length (no half-cycle correction) was applied to ensure all costs and quality-adjusted life years (QALYs) were captured.

Figure 4.1: Model structure



Based on Figure 14 of the CS[2]
CS = company submission

EAG comment: The main concerns of the EAG relate to: a) the appropriateness of aggregating tumour sites, and b) the use of a PSM without exploring a state transition model approach alongside it.

a) Following the separate modelling of each tumour site, populations were aggregated to generate outcomes across all tumour sites. Clarification question (CQ) B1 1. questioned the appropriateness of aggregating the results, given substantial heterogeneity across each tumour site. In response, the company suggest that it is highly plausible that MSI-H/dMMR status is a significant driver of

efficacy outcomes, and consequently derive that there exists a case for considering a multi-cohort structure that both captures cohort specific results and provides results that reflect the overall population covered in the licensed indication. While the company justify the poor prognosis associated with MSI-H/dMMR status, heterogeneity across tumour sites endures. Further, the MSI-H/dMMR status is only known for the intervention population and thus, aggregating comparator populations is even more questionable. It remains unclear as to why aggregating results is deemed appropriate, however, the EAG recognises that tumour site specific base-case results are also displayed in the CS.

b) The NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19 recommends the use of state transition models (STMs) alongside PSMs to verify the plausibility of PSM extrapolations and to explore key clinical uncertainties in the extrapolation period.[32] Clarification question B1 2. requested justification as to the use of a partitioned survival approach given that, in KEYNOTE-158, the TTD utility modelling does not appear to be aligned with the utilised model structure. Further, the EAG requested that state transition modelling is used to verify the plausibility of the PSM extrapolations, and to address uncertainty in the extrapolation period. In response the company suggest that, given the availability of data for pembrolizumab and the comparators, no strong case exists for an STM approach mitigating the limitations to PSM approach outlined in TSD 19. That is, the company suggest the data requirements for an STM could not be met and, as such, differences in approach would be superficial in practice. Additionally, the company argue that the drawbacks to the PSM approach have been addressed within the CS and clarification letter responses in accordance with the information/scenarios recommended in TSD 19 and that submitting two model types is uncommon in oncology appraisals.

4.2.3 Population

In line with the final NICE scope, the marketing authorisation and the populations in the KEYNOTE-164 and KEYNOTE-158 trials, the populations considered in the CS were the below MSI-H or dMMR solid tumours in adults. Although, within the economic model, the MSI-H/dMMR status is unknown for patients in the comparator arm, with the exception of paclitaxel in the gastric tumour site and chemotherapy of physicians choice (paclitaxel/doxorubicin) in the endometrial tumour site.

- Unresectable or metastatic colorectal cancer (mCRC) after previous fluoropyrimidine-based combination therapy
- Advanced or recurrent endometrial carcinoma, who have diseased progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation
- Unresectable or metastatic gastric cancer, small intestine cancer or biliary cancer, who have disease progression on or following at least one prior therapy.

The patient populations included in the economic model for the intervention reflected those included in single-arm trials KEYNOTE-164 and KEYNOTE-158. Without knowledge of the MSI-H/dMMR status for most of the comparator populations, it is unclear whether these populations reflected those included in the KEYNOTE trials. For paclitaxel in gastric cancer {Chao, 2021 #118}, and for treatment of physicians choice (paclitaxel/doxorubicin) in endometrial cancer {Makker, 2022 #110}, the informing data sources included MSI-H/dMMR selected patients, respectively. Patient populations for the intervention and comparators corresponded to the five tumour sites included in the economic model:

- Colorectal cancer (KEYNOTE-164)
- Endometrial cancer (KEYNOTE-158)
- Gastric cancer (KEYNOTE-158)

- Small intestine cancer (KEYNOTE-158)
- Cholangiocarcinoma (biliary cancer, KEYNOTE-158)

The ASaT population was used when analysing the survival outcomes for pembrolizumab, consisting of all allocated participants that received at least one treatment dose.

EAG comment: The main concerns of the EAG relate to: a) the lack of MSI-H/dMMR status for most comparators, and b) the use of the ASaT populations of KEYNOTE-158 and KEYNOTE-164.

a) The MSI-H/dMMR status of comparator populations included in the economic model was largely unknown. Using these populations alongside pembrolizumab trials (within the MSI-H/dMMR population) may influence the relative effectiveness. The company argue that the approach was conservative as MSI-H/dMMR is potentially a negative prognostic factor, however, also suggest that MSI-H/dMMR status is a treatment effect modifier for immunotherapies (i.e., more efficacious in MSI-H/dMMR patient, ceteris paribus). The impact on the relative effectiveness of the unknown MSI-H/dMMR status of the comparator populations remains uncertain. More details of the EAG's view on this issue are described in Sections 3.4.3 and 4.2.6 of this report.

b) In the CS, analyses of pembrolizumab survival outcomes were conducted using the ASaT populations of KEYNOTE-158 and KEYNOTE-164. The intention-to-treat (ITT) population is more commonly used to analyse survival outcomes as this population provides a more realistic representation of the population that would be treated in practice, including patients who may have dropped out of the study or not adhered to the treatment protocol. Further, it was unclear whether the ASaT or ITT populations were used to assess comparator survival outcomes. In response to the clarification letter, the company highlight that all participants, post-screening, were given at least one dose of the intervention and were therefore included in the analysis. The EAG accepts the company's response as the same efficacy results would be expected if the ITT population had been used.

4.2.4 Interventions and comparators

The intervention considered in the CS was pembrolizumab (200 mg) administered intravenously (IV) every three weeks for up to 35 cycles, or until disease progression. In the single-arm KEYNOTE-164 and KEYNOTE-158 trials, patients that had been treated with at least eight doses of pembrolizumab could discontinue treatment. Further, patients for whom disease progressed, but still experienced clinical benefits (without additional increase in tumour burden), could continue treatment. This was reflected in the economic model.

The comparator considered in the CS was SoC, which differed per tumour site and, as such, was (in most cases) applied as a basket of treatments. The modelled comparators in the CS deviated from those included in the final NICE scope, as summarised in Table 4.4 below. The company suggested that no direct comparators existed in the same overall indication, and that treatment options available for MSI-H/dMMR solid tumours were limited. As such, the company sourced comparators from UK treatment guidelines, and validated these with clinical experts. Identified comparators were used to inform the clinical SLR, to identify published evidence to inform the economic model. The MSI-H/dMMR status of patients was largely unknown for comparators. The company considered this to be a conservative approach for estimating the relative effectiveness for pembrolizumab, suggesting that MSI-H/dMMR status is associated with a poorer prognosis. As no evidence could be identified for FOLFIRI/FOLFOX in small intestine cancer, nab-paclitaxel was used as a proxy chemotherapy. Distributions were informed by a consensus opinion of market shares and varied probabilistically.

Table 4.4: Treatment comparators included in the economic model and final NICE scope

Tumour site	Included comparator treatments			
	Final NICE scope	Modelled treatment comparators		
		Treatment		Dose/frequency
Colorectal cancer	Established management without pembrolizumab	Pooled FOLFIRI/FOLFOX	Folinic acid	400 mg/m^2 every 2 weeks
	Nivolumab with ipilimumab		Oxaliplatin	85 mg/m^2 every 2 weeks
	Single-agent irinotecan (after FOLFOX)		Fluorouracil	1000 mg/m2 every 2 weeks
	FOLFIRI (after either FOLFOX or CAPOX)	Trifluridine-tipiracil (TAS-102)		35 mg/m^2 Twice daily on days 1-5 and 8-12 of 28-day cycle
	Raltitrexed (if 5-fluororacil and folinic acid are not suitable)			
	Trifluridine-tipiracil (TAS-102)			
Endometrial cancer	Established management without pembrolizumab	Chemotherapy (physician's choice of paclitaxel or doxorubicin)	Paclitaxel	80 mg/m^2 Once per week, for 3 weeks of a 4-week cycle
	Chemotherapy, including: - Carboplatin and paclitaxel - Paclitaxel monotherapy - Doxorubicin monotherapy - Carboplatin monotherapy		Doxorubicin	60 mg/m^2 Every 3 weeks
	Hormone therapy (such as medroxyprogesterone acetate and megestrol)			
Gastric cancer	Established management without pembrolizumab	Paclitaxel		80 mg/m^2 Once per week, for 3 weeks of a 4-week cycle
Small intestine cancer	Established management without pembrolizumab	Nab-paclitaxel	Folinic acid	400 mg/m^2 every 2 weeks
			Oxaliplatin	85 mg/m^2 every 2 weeks
			Fluorouracil	1000 mg/m^2 every 2 weeks
Cholangiocarcinoma (biliary cancer)	Established management without pembrolizumab	mFOLFOX	Oxaliplatin	100 mg/m^2 every 2 weeks
			Fluorouracil	2400 mg/m^2 every 2 weeks

Tumour site	Included comparator treatments			
	Final NICE scope	Modelled treatment comparators		
		Treatment		Dose/frequency
			Folinic acid	100 mg/m^2 every 2 weeks

FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; NICE = National Institute for Health and Care Excellence; TAS-102 = tipiracil hydrochloride

EAG comment: The main concerns of the EAG relate to: a) the use of treatment baskets to form SoC as the comparator, and b) comparators listed in the NICE scope that were not considered in the current submission.

a) To reflect SoC, the company applied treatment comparators as a basket of treatments that varied between the different tumour sites. It seems to the EAG that the SoC simply comprised comparators for which evidence was available, sometimes using a single comparator, sometimes using a pooled comparator (without weighting, e.g., pooled FOLFIRI/FOLFOX for colorectal cancer). It is unclear whether comparator baskets are a realistic representation of UK clinical practice. Costs and health outcomes of the SoC arm were weighted using market share estimates to generate results within each tumour site. The comparator effectiveness and costs are therefore based on the average clinical effectiveness and weighted average costs across the treatments included in the comparator basket, which may potentially underestimate SoC. The fully incremental results per tumour site also seem to indicate this, as in all SoC baskets one comparator is (extendedly) dominated. Therefore, in addition to the results for the overall indication, the EAG presents the fully incremental EAG base-case results per tumour site.
b) The comparators included in the economic evaluation were not aligned with those presented in the final NICE scope. Nivolumab plus ipilimumab, irinotecan plus raltitrexed, and established clinical management (ECM) were not included by the company in the decision problem, despite designation in the NICE scope as relevant comparators. In the clarification letter, the EAG requested justification as to the appropriateness of each excluded treatment comparator and to evidence deviation from the final scope for each tumour site. In response, the company suggested that deviations were based on clinical opinion and consensus from previous appraisals within the relevant tumour sites. The EAG do not think that the rationale provided for exclusion is sufficiently robust. The EAG's view on discrepancies between the considered comparators and the NICE scope is described in more detail in Section 2.3 of this report.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the National Health Service (NHS) and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is one week with a lifetime time horizon (40 years). No half-cycle correction has been applied.

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence to inform the treatment effectiveness of pembrolizumab were the KEYNOTE-158 (colorectal cancer [n=124]) and KEYNOTE-164 (endometrial [n=83], gastric [n=51], small intestine [n=27] and biliary cancer [n=22]) single-arm trials. Data correspond to the 19 February 2021 cut-off date for KEYNOTE-164 and the 15 October 2021 cut-off date for KEYNOTE-158. Published studies identified from the clinical SLR were used to inform survival analyses of SoC. All

comparators except paclitaxel (gastric cancer) and paclitaxel/doxorubicin (endometrial cancer) did not consider the MSI-H/dMMR status of patients.

In order to evaluate the cost effectiveness of the overall indication in the company's base-case, the results from individual tumour sites were aggregated based on the number of patients within each tumour site of the KEYNOTE-158 and KEYNOTE-16 trials. Tumour site distribution based on UK cancer incidence data from published literature was explored in a scenario analysis (CS, Table 43). The data was adjusted to account for the proportion of patients at different disease stages and then calculate the total eligible population for each tumour site.

The main outcomes for treatment effectiveness were OS, PFS and TTD. Analyses of the survival outcomes of pembrolizumab were performed using the ASaT populations (all participants who received at least one dose of treatment) of KEYNOTE-158 and KEYNOTE-164. Considering the heterogeneity between patients across multiple tumour sites, the company considered both Bayesian hierarchical models (BHMs) and standard parametric modelling independent of tumour sites for the modelling of pembrolizumab OS and PFS.

Standard parametric curves were fitted to the KM data for the extrapolation of OS and PFS. The generalised gamma curve was not explored for the BHM approach because of convergence issues. Suitability was evaluated by visual inspection to assess the visual fit of the curve to the KM data, statistical fit of the curve to the KM data using goodness-of-fit criteria (AIC, BIC, DIC), validation against published long-term survival data, and clinical plausibility for short and long-term survival based on clinical expert validation. According to the CS, the curves selected to predict OS and PFS for pembrolizumab were consistent with the clinical consensus that a proportion of patients across different tumour sites will be functionally cured around 5 years after treatment and their probability of death after that is similar to that of the general population.

4.2.6.1 Pembrolizumab

The company used BHM to model OS and PFS of pembrolizumab in its base-case. The approach assumes similar intervention outcomes across tumour sites, with no predetermined order of effectiveness. The company considered that BHM constitute a balance between assuming complete independence between tumour sites and complete homogeneity (pooling all tumour sites data together). The company also considered that BHM captures the heterogeneity between different tumour sites and allows the borrowing of relevant information across groups or "baskets" by utilising shared parameters. This approach, according to the CS, increases estimate precision by analysing baskets together, and reduces implausible estimates for tumour sites with few patients.

The BHM approach combines both fixed effects that are shared by all tumour sites, and tumour site-dependent parameters that capture the heterogeneity of outcomes observed. Fixed-effects covariates, including age, gender, ECOG score, cancer stage, and number of prior lines of therapy, were selected based on clinical expert opinion and exploratory analysis of available data.

The company also explored piecewise BHM models for the modelling of PFS in a scenario analysis due to the poor fit of the one-piece models to the observed Kaplan–Meier data from 0-10 weeks. Additional scenario analyses explored standard parametric models in which tumour site was treated as a standalone trial. This approach assumed independence between tumour sites, not allowing for survival data borrowing across sites, and hence according to the company the uncertainty was higher than under the BHM approach.

For the modelling of TTD, the company stated that the mature pembrolizumab TTD data collected from KEYNOTE-164 and KEYNOTE-158 allowed for direct incorporation of the KM function into the model.

4.2.6.2 Standard of care

The company considered various methods to derive comparative efficacy of pembrolizumab versus comparators, including HRs derived from ITC and MAICs, independently fitted parametric curves to comparator KM curves and non-responder analysis. The company in the end modelled comparator OS and PFS using independently fitted parametric survival curves, considering that 1) the proportional hazards assumption was violated in all cases, 2) the impact of population adjustment for observed confounders (via MAIC) was negligible and 3) flexible methods to derive time-varying HRs were not feasible.

Time to treatment discontinuation data for the selected comparators were not available. Therefore, an exponential model was fitted to the median ToT, or if the median ToT was not reported, PFS was used as a proxy for PFS (supported by clinical experts).

A summary of methods explored by the company to model pembrolizumab, and comparator efficacy was shown in CS, Tables 44 and 45.

To illustrate the company's considerations for their choice of survival curves for the modelling of OS and PFS of pembrolizumab and SoC, Table 4.5 is shown below including the CRC tumour site as an example for the comparator treatments informing SoC. Considerations informing the company's choice of survival curves for comparators in other tumour sites were similar.

4.2.6.3 Overall survival

The company selected the log-normal curve for the modelling of pembrolizumab OS in its base-case based on statistical fit, comparison of the observed versus the predicted hazard functions, clinical expert opinion, and visual fit to the KM data.

For comparator treatments, the company's base-case OS curves were mainly selected based on their visual and statistical fit to the KM data, and clinical expert validation. As shown in CS Table 52, log-logistic curves were selected for the OS modelling of TAS-102 and pooled FOLFOX/FOLFIRI (CRC), log-normal curves for the OS modelling of paclitaxel/doxorubicin (endometrial cancer), mFOLFOX and mFOLFIRI (both cholangiocarcinoma), Weibull curves for the OS modelling of FOLFIRI (gastric cancer) and nab-paclitaxel (small intestine cancer), and a Gompertz curve for the OS modelling of paclitaxel (gastric cancer).

4.2.6.4 Progression-free survival

The company selected the log-normal model for the modelling of pembrolizumab PFS in its base-case based on visual and statistical fit to the KM data and clinical expert opinion.

For comparator treatments, the company's base-case PFS curves were mainly selected based on their visual and statistical fit to the KM data, clinical expert opinion and validation with published data. As shown in CS Table 59, log-logistic curves were selected for the PFS modelling of TAS-102 and pooled FOLFOX/FOLFIRI (CRC), Gompertz curves were selected for the PFS modelling of paclitaxel/doxorubicin (endometrial cancer), paclitaxel and FOLFIRI (gastric cancer), log-normal curves were selected for the PFS modelling of mFOLFOX and mFOLFIRI (cholangiocarcinoma), and a Weibull curve was selected for the PFS modelling of nab-paclitaxel (small intestine cancer).

4.2.6.5 Time to treatment discontinuation

The company directly used TTD KM data from the KEYNOTE-164 and KEYNOTE-158 trials (not combined across tumour sites) in its base-case for the modelling of pembrolizumab TTD. The company stated that the model limits pembrolizumab treatment to 35 costed cycles and argued that this is consistent with the clinical trial protocols, the approved label and previous NICE appraisals (TA709[33], TA531 [33]and TA683[33]).

As stated above, TTD data for the selected comparators were largely unavailable. Therefore, an exponential model was fitted to the median ToT, or if the median ToT was not reported, PFS was used as a proxy for TTD (supported by clinical experts).

4.2.6.6 Background mortality

General population mortality was estimated from the most recent version of the national life tables for England and Wales and calculated separately for each tumour site based on KEYNOTE-164 or KEYNOTE-158 trial's age and gender distribution.

4.2.6.7 Treatment waning

In order to reflect the recommendations of EAGs in previous appraisals of pembrolizumab and present a conservative estimate of the economic value of pembrolizumab, the company implemented waning of the pembrolizumab treatment effect occurring between 7 and 9 years from the start of treatment. The company chose this starting point because the KM curves for pembrolizumab, in all tumour sites, extend beyond 5 years and therefore a time point of 2 years past the end of the observed trial period was selected for initiation of treatment effect waning (which has become a common convention in oncology appraisals). A scenario analysis was provided without the implementation of treatment waning.

Table 4.5: Company's considerations for their selection of survival curves

	OS	PFS
Statistical fit to the observed data (based on AIC, BIC, DIC)	Pembrolizumab (aggregated tumour sites): The DIC indicates that the log-normal has the best statistical fit followed by the log-logistic (7 points difference). TAS-102 (colorectal cancer): The AIC and BIC indicate that the log-logistic has the best statistical fit followed by the generalised gamma (7 points AIC and 11 points BIC difference). Pooled FOLFOX/FOLFIRI (colorectal cancer): The AIC and BIC indicate that the log-logistic has the best statistical fit.	Pembrolizumab (aggregated tumour sites): The DIC indicates that the log-normal has the best statistical fit. TAS-102 (colorectal cancer): The AIC indicates that the generalised gamma has the best statistical fit. The BIC indicates that the log-logistic has the best statistical fit. Pooled FOLFOX/FOLFIRI (colorectal cancer): The AIC and BIC indicate that the log-logistic has the best statistical fit.
Visual fit to the observed data	Pembrolizumab (aggregated tumour sites): Not explicitly discussed. TAS-102 (colorectal cancer): Not explicitly discussed. Pooled FOLFOX/FOLFIRI (colorectal cancer): Not explicitly discussed.	Pembrolizumab (aggregated tumour sites): Visually, the base-case curve does not fit the observed pembrolizumab PFS data very well: the CRC curve appears to overestimate PFS from 6 to 18 months and thereafter underestimates PFS; observed plateaus in KM data for CRC, gastric and small intestine tumour sites are not captured in the extrapolations; and there is apparent underestimation of endometrial PFS. A piecewise BHM model was explored to extrapolate pembrolizumab PFS outcomes from 10 weeks onwards.

	OS	PFS
		TAS-102 (colorectal cancer): Not explicitly discussed. Pooled FOLFOX/FOLFIRI (colorectal cancer): Not explicitly discussed.
Clinical plausibility of the survival estimates based on validation against published long-term survival data	Pembrolizumab (endometrial cancer): The observed survival data showed a close alignment between 0 and 15 years, when compared to Thurgar (2021) for women with previously treated MSI-H/dMMR unresectable or metastatic endometrial cancer. Pembrolizumab (gastric cancer): Survival estimates were deemed to be conservative when compared to Bellone (2022). TAS-102 (colorectal cancer): Not explicitly discussed. Pooled FOLFOX/FOLFIRI (colorectal cancer): Not explicitly discussed.	Pembrolizumab (endometrial cancer): Survival estimates were lower than those reported in Thurgar (2021). Survival estimates were deemed to be conservative when compared to Bellone (2022). Pembrolizumab (gastric cancer): Survival estimates aligned with estimates from Lauren (2020) for second-line metastatic gastric cancer. TAS-102 (colorectal cancer): Not explicitly discussed. Pooled FOLFOX/FOLFIRI (colorectal cancer): Not explicitly discussed.
Clinical plausibility of the survival estimates based on clinical expert validation	Pembrolizumab (aggregated tumour sites): Clinical experts highlighted that the log-normal, log-logistic and Weibull resulted in plausible survival projections, and that the exponential and Gompertz were overly pessimistic as they do not capture the favourable outcomes expected in the functionally cured population. TAS-102 (colorectal cancer): UK clinical experts validated the selected curves and confirmed that extrapolations were clinically plausible. Pooled FOLFOX/FOLFIRI (colorectal cancer): UK clinical experts validated the selected curves and confirmed that extrapolations were clinically plausible.	Pembrolizumab (aggregated tumour sites): Clinical experts highlighted that the log-normal, log-logistic and Weibull were plausible curves, with the exponential and Gompertz being implausible and too pessimistic as they do not capture the functionally cured population. TAS-102 (colorectal cancer): Not explicitly discussed. Pooled FOLFOX/FOLFIRI (colorectal cancer): Not explicitly discussed.
Base-case approach	Pembrolizumab (aggregated tumour sites):	Pembrolizumab (aggregated tumour sites):

	OS	PFS
	Log-normal TAS-102 (colorectal cancer): Log-logistic Pooled FOLFOX/FOLFIRI (colorectal cancer): Log-logistic	Log-normal TAS-102 (colorectal cancer): Log-logistic Pooled FOLFOX/FOLFIRI (colorectal cancer): Log-logistic

Source: CS section B.3.3.[2] and response to the request for clarification
AIC = Akaike information criterion; BIC = Bayesian information criterion; CRC = colorectal cancer; CS = company submission; DIC = deviance information criterion; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin; KM = Kaplan-Meier; MSI-H = microsatellite instability-high; OS = overall survival; PFS = progression-free survival; PPP = Platinum pre-treated population; TAS-102 = tipiracil hydrochloride; ToT = Time on treatment; UK = United Kingdom

EAG comment: The main concerns of the EAG relate to: a) methodological uncertainty regarding the analysis of relative effectiveness of pembrolizumab, b) the use of BHM for OS and PFS for pembrolizumab, c) trial-based approach to inform tumour site distribution, d) lack of survival curve choice transparency, and e) the modelling of comparators TTD.

a) The company stated that except for paclitaxel in gastric cancer and paclitaxel/doxorubicin in endometrial cancer, patients in comparator studies were not selected by MSI-H/dMMR status. The company argued that this is likely to result in conservative estimates of relative effectiveness for pembrolizumab, given MSI-H/dMMR status is associated with a poorer prognosis. However, the uncertainty about the effect of MSI-H status has been highlighted as a key issue in Section 3.4.3 of this report. Therefore, the EAG considers the current estimation of the relative effectiveness of pembrolizumab to be uncertain. A study of Briggs[34] explored alternatives for assessing the cost effectiveness of tumour-agnostic therapies that rely on single-arm basket trials, including direct comparison of the intervention with a literature-based cohort, an intracohort comparison, and a non-responder analysis. The non-responder alternative was also mentioned in the CS, but the company did not formally consider this approach in their economic analysis because 1) there is little evidence to suggest that non-responders are a suitable surrogate for comparator OS and PFS outcomes in this indication, and 2) due to the small patient numbers and exacerbated by the high level of disease response demonstrated by pembrolizumab, there were few non-responder patients to collect data from for this approach. The EAG acknowledges that the non-responder analysis would be based on strong assumptions (assuming patients treated with pembrolizumab from KEYNOTE-158 and KEYNOTE-164 who do not achieve a partial or complete response have survival outcomes that are consistent with patients who received a comparator treatment within established clinical practice). However, the company's argument that there were few non-responding patients in KEYNOTE-158 and KEYNOTE-164 does not seem to be valid, given that in these trials only 34.3% and 33% of patients respectively had an objective response. Despite the strong underlying assumption, the EAG explored the non-responder analysis in a scenario analysis to provide the committee cost effectiveness results based on estimation of the OS and PFS relative effectiveness of pembrolizumab in patients that all had a positive MSI-H/dMMR status. In absence of NICE DSU TSD 14 details on the optimal parametric curves to extrapolate the non-responder OS and PFS KM data, these were extrapolated using the standard parametric curves with the best statistical fit (based on AIC, a functionality in the economic model). The results of the EAG's scenario analyses indicated that the non-responder approach also affects the modelled life years and QALY gains of pembrolizumab

(increases or decreases, depending on the tumour site). As this is not necessarily in line with the EAG's expectations, the EAG would like the company to provide further details on how the non-responder analysis was implemented into the economic model, and to elaborate on how this analysis also affects the modelled pembrolizumab life years and QALY gains. Finally, the EAG also would like to note that an additional advantage of the non-responder analysis is that the relative effectiveness estimate of pembrolizumab was not subject to potential biases related to comparing single-arm trials to external controls. On balance, there are limitations associated with both approaches, and both approaches should be considered in decision-making.

b) The company used a BHM approach to model pembrolizumab OS and PFS to capture heterogeneity between outcomes of the different tumour sites. A scenario analysis was performed modelling pembrolizumab OS and PFS using standard parametric models independent of tumour sites. The EAG considers that the BHM approach would only be appropriate if the assumption that the different tumour sites can be considered subgroups of an overarching MSI-H/dMMR solid tumour population is justified. The EAG acknowledges the advantage of the BHM approach allowing information to be borrowed between tumour sites, given their small individual sample sizes. However, considering the observed differences in terms of survival outcomes (OS, PFS), there seems to be substantial heterogeneity between the individual tumour sites. By applying BHM, tumour site-specific survival estimates are pulled to an overall average, which biases the survival estimates on individual tumour site level. Nevertheless, modelling of individual tumour sites using small sample sizes likely also introduces bias. In addition, the EAG questioned pooling data of the KEYNOTE-158 and KEYNOTE-164 trials and suggested to model these separately. In line with this, in the minutes of the company's advisory board meeting it is stated that "[redacted]". Hence, the EAG questions the suitability of the BHM approach in the context of this submission and considers this a key issue. The company should apply the BHM approach only to comparable tumour sites, justified and supported by clinical arguments and evidence rather than statistical arguments. Following the comments of the health economics advisor during the advisory board, an updated model and scenario analyses should be provided by the company modelling the KEYNOTE-164 data for the colorectal cancer tumour site separately and applying the BHM approach only to the tumour sites included in the KEYNOTE-158 basket trial. In addition, the company should elaborate further on the suitability of the BHM approach for time-to-event outcomes rather than response outcomes.

c) The company used the number of patients included within each tumour site of the KEYNOTE-158 and KEYNOTE-164 trials to inform the distribution of tumour site inputs in the economic model. The company justified this trial-based approach stating that it was difficult to accurately estimate real-world distributions across tumour sites. Although the EAG understands this potential difficulty, it questions the plausibility of informing tumour site distribution based on the two KEYNOTE trials. Recruitment of patients to trials is not necessarily representative of real-world incidence, especially when recruitment occurs for two different trials. The EAG therefore considers that the trial-based approach of distributing tumour site inputs in the economic model is potentially driven by differences between the KEYNOTE trials that may not be reflective of UK clinical practice. Alternatively, the EAG prefers informing tumour site distribution based on UK epidemiological data, as was explored by the company in a scenario analysis, and adopted this approach in its base-case.

d) The EAG considered the company's choice of survival curves for the modelling of treatment effectiveness in the health economic model as lacking details regarding the NICE DSU TSD 14 criteria. The company stated that suitability of survival curves was evaluated by the visual and statistical fit of the curves to the KM data, validation against published long-term survival data, and clinical plausibility for short and long-term survival based on clinical expert validation. However, although the company presented figures including the KM data and extrapolated survival curves, the visual fit of the survival curves to the observed data was not explicitly discussed (except the visual fit of the company's base-case curve to extrapolate pembrolizumab PFS). In addition, validation against published long-term survival data was limited to endometrial and gastric cancer only. In response to clarification question B9, the company stated that "*finding relevant literature with published survival curves in patients with MSI-H/dMMR disease was limited and validation was only possible for the endometrial and gastric tumour sites*". Next to that, the company provided some details on what clinical experts stated during the UK advisory board about the suitability of the survival curves to extrapolate pembrolizumab OS and PFS, but these details for the comparators are limited to "*UK clinical experts validated the selected curves and confirmed that extrapolations were clinically plausible*". For full transparency of clinical expert input, the full UK advisory board meeting minutes should be shared with the EAG. Finally, the company in a scenario analysis explored standard parametric modelling independent of tumour sites for the modelling of pembrolizumab OS and PFS as an alternative to their base-case BHM approach. Although goodness-of-fit statistics, plots of KM data and the extrapolated curves and hazard plots were provided in Appendix J, explicit justification of curve choices based on guidance from NICE DSU TSD 14 and 21 was lacking. In response to clarification question B6, a table including a general rationale was provided, but the EAG would like to see more specific details in terms of clinical plausibility based on clinical expert opinion.
e) Published TTD KM-data were unavailable for most comparators and the company therefore either fitted an exponential distribution to the reported median ToT, or PFS was used as a proxy for TTD if the median ToT was not reported. In response to clarification question B11, the company provided scenario analyses using PFS as a proxy for all comparator TTD outcomes. Results showed that PFS as a proxy may overestimate TTD for some comparators where the available published data suggests some patients would discontinue therapy prior to progression. The EAG therefore considers the company's approach of fitting an exponential distribution to the reported median ToT for those comparators of which the median ToT was reported, to be conservative.

4.2.7 Adverse events

Adverse events were modelled for pembrolizumab and all comparators. For pembrolizumab, grade 3+ AEs with an incidence equal to or greater than 1% were included (incidences were based on KEYNOTE-164 for CRC and on KEYNOTE-158 for all other tumour sites [CS Table 62]). For the comparators, grade 3+ AE with an incidence equal to or greater than 3% were included (incidences were based on studies identified by an SLR). for all comparators. Adverse events disutilities were not included in the company base-case as they were assumed to be captured within the modelled utilities. The company's scenario analysis including AE disutilities resulted in only a small change to the NHB and ICER. In the company base-case, AE costs were sourced from the NHS Reference costs applied as a one-off at model start for one cycle duration (Table 4.6).[35]

EAG comment: The EAG has no concerns relating to the incidence or implementation of adverse events.

4.2.8 Health-related quality of life

4.2.8.1 Health-related quality of life data identified in the review

An SLR identified 16 studies including utility values for the population relevant for this technology appraisal. Only Grothey 2013[1] was used as a source of evidence in the CS.

4.2.8.2 Implementation of health-related quality of life in the model

Health-related quality of life (HRQoL) in the KEYNOTE-158 trial was assessed in every treatment cycle for the first four cycles, then every three cycles until 9 months and then every four cycles until disease progression. After progression, HRQoL was measured at the treatment discontinuation visit and for a proportion of patients at the 30-day safety follow-up visit. HRQoL was not measured in KEYNOTE-164. All utilities were age-adjusted using a utility multiplier.

The HRQoL of endometrial cancer, gastric cancer, small intestine cancer and cholangiocarcinoma was modelled using a time-to-death approach based on a linear mixed-effect regression model using utility data from KEYNOTE-158. The utility values that resulted from the time-to-death analysis are shown in Table 4.6) Scenario analyses were conducted applying health-state (progression status) based utilities (Table 4.7). As HRQoL was not measured in KEYNOTE-164, utility values for the colorectal cancer tumour site were modelled using health-state dependent utilities from the literature (Grothey 2013[1], Table 4.7).

4.2.8.3 Disutility values

Adverse events disutilities were not included in the company base-case as they were assumed to be captured within the modelled utilities. The company explored including AE disutilities in a scenario analysis.

Table 4.6: Time to death utility values

Time to death	Mean utility value
360+ days	[redacted]
180-159 days	[redacted]
90-179 days	[redacted]
30-89 days	[redacted]
<30 days	[redacted]

Based on Table 66 of the CS[2]
CS = company submission

Table 4.7: Health state-based utility values

Health state	Colorectal cancer utility	Endometrial cancer utility (scenario)	Gastric cancer utility (scenario)	Small intestine cancer utility (scenario)	Cholangiocarcinoma (scenario)
PFS: on treatment	0.73	0.721	0.708	0.814	0.805
PFS: off treatment	0.74				
Progressed disease	0.59	0.667	0.654	0.737	0.702

Health state	Colorectal cancer utility	Endometrial cancer utility (scenario)	Gastric cancer utility (scenario)	Small intestine cancer utility (scenario)	Cholangiocarcinoma (scenario)
Based on Tables 67 and 68 of the CS[2] CS = company submission; PFS = progression-free survival					

4.2.8.4 Adverse event utilities

Adverse event disutilities were not included in the company base-case as they were assumed to be captured within the modelled utilities. The company's scenario analysis including AE disutilities resulted in only a small change to the NHB and ICER.

EAG comment: The main concerns of the EAG relate to a) the plausibility of the time-to-death approach for the modelling of HRQoL in tumour sites of the KEYNOTE-158 basket trial, b) the chosen utility source for the modelling of HRQoL in the colorectal cancer tumour site and c) assumptions related to the implementation of adverse event utilities.

a) The company used a time-to-death utility approach to model the HRQoL of tumour sites included in KEYNOTE-158. The company argued that this approach accurately depicts the declining quality of life patients may experience as they move closer to death and stated that the conventional health state approach does not account for variation in quality of life from the time of progression through to terminal care. The EAG questions the validity of the time-to-death approach for several reasons. Firstly, contrary to the more established method of using progression status to estimate utility values, the time-to-death approach for the modelling of HRQoL is not mentioned in the NICE TSD guidance on utilities. As no reference to any guidance was made in the company submission the EAG requested this in its clarification letter, but the company did not respond to this request. Next to that, the time to death utility approach seems inconsistent with the progression-based model structure, which suggests that the main differences in costs and effects between pembrolizumab and the comparators were expected to be captured by disease status (i.e., progression-free and progressed disease) rather than time to death. Given the increased post-progression survival with pembrolizumab, the use of time-to-death utilities favours pembrolizumab. In addition, there was a lack of details provided for the statistical analyses that were conducted to attain the time-to-death categories and utilities used in the time-to-death approach. In the CS, apart from a statement that linear mixed effects models were fitted to account for repeated measures, no further details were provided. Therefore, the company should provide the full statistical analyses details for the various models that were considered. The time-to-death approach also lacks face validity. A relatively high utility value of [redacted] was modelled for the 360+ days to death category, which seems unrealistically high for patients with advanced or metastatic disease and particularly favours pembrolizumab given the increased survival (and hence time spent in this category) in these patients. The EAG acknowledges that the health state-based progression-free utility values for small intestine cancer and cholangiocarcinoma also seem high. However, the impact of this is likely smaller in the health state-based approach compared to the time to death approach as disease progression is likely to happen sooner than reaching the last year of life. Next to that, the time to death utility approach also seemed to lack face validity as it did not distinguish between tumour sites, whereas health-state based utilities differed by up to [redacted] and [redacted] between tumour sites in the progression-free and progressed disease health states respectively.
Based on these considerations, the EAG preferred the more conservative health state-based approach of modelling utilities as a function of progression status rather than time to death and adopted this approach in its base-case.

b) The company identified 16 publications reporting utility values in colorectal cancer and selected utility values from Grothey 2013[1] to model the health-state based utilities in colorectal cancer. When requesting justification for preferring the utility values from Grothey 2013[1] over utility values from other identified studies in clarification question B19, the company responded that using the utilities from Grothey 2013[1] was conservative as it reported the lowest PFS and PPS utilities. Nevertheless, the EAG would like to see additional scenario analyses exploring PFS and PPS utilities from other identified studies to demonstrate that informing HRQoL in colorectal cancer based on Grothey 2013[1] is indeed conservative.
c) The company assumed that utility measurements for the estimation of HRQoL would likely capture the impact of AEs and therefore did not apply AE disutilities in the company base-case. The EAG questions this assumption, because after the first four weeks HRQoL was measured a maximum of once every three weeks. In contrast, the company assumed that most (84 out of 95) of the AEs had a duration of seven days. If this assumption is correct, many AEs may not be captured by the utility measurement. The company explored a scenario analysis including AE disutilities, assuming for the majority of AEs that the disutility was the 'assumed average utility decrement of recorded utilities'. The only information identified by the EAG to support these assumptions was a statement in the economic model. The EAG therefore considers the application of AE disutilities and their duration untransparent, adding uncertainty to the economic model. The impact of this issue, however, is likely minor.

4.2.9 Resources and costs

The cost categories which were included were drug acquisition costs, drug administration costs, subsequent treatment costs, health state costs, adverse event costs and end-of life costs. Unit prices were based on the drugs and pharmaceutical electronic market information tool (eMIT) [36], the Monthly Index of Medical Specialities (MIMS)[37], NHS Reference Costs[35] as well as studies identified in the literature review. Costs were inflated to 2020/21 prices using the Personal Social Services Research Unit (PSSRU) inflation indices where necessary.

4.2.9.1 Resource use and costs data identified in the review

The SLR identified 20 studies that reported relevant healthcare resource use. Some of these studies were used to inform resource use, and to validate model assumptions.

4.2.9.2 Pembrolizumab

Pembrolizumab is offered at a list price of £2,630.00 per single pack of 4 ml with 25 mg/ml. In accordance with the market authorisation and the KEYNOTE-158 and KEYNOTE-164 trials, 200 mg of pembrolizumab were modelled to be administered intravenously every 3 weeks until discontinuation. The model accounts for relative dose intensity (RDI) which is tumour site dependent.

4.2.9.3 Comparator costs

Each drug in the SoC arm was modelled separately. When aggregated into one basket weights based on expert opinion were used. An RDI of 100% was assumed for all comparators, except for tipiracil hydrochloride (TAS-102) where an RDI of 89% was assumed. Information about the pack cost, dosing schedule and cost per administration was reported in CS Tables 73, 74 and 75 respectively.

4.2.9.4 Subsequent treatment

A proportion of patients who progressed in the model received subsequent treatment. The proportion of patients that received subsequent treatment, the duration and distribution of therapies across tumour

sites were based on data from the KEYNOTE-164 and KEYNOTE-158. The proportion of patients that received subsequent treatments was: 26.64%, 22.89%, 19.61%, 40.74% and 33.33% for colorectal cancer, endometrial cancer, gastric cancer, small intestine cancer and cholangiocarcinoma tumour sites, respectively. The duration of subsequent treatment was [redacted] and [redacted] days for colorectal cancer, endometrial cancer, gastric cancer, small intestine cancer and cholangiocarcinoma tumour sites, respectively. The distribution of subsequent treatments across tumour sites is shown in Table 4.8

Table 4.8: Distribution of subsequent therapies across tumour sites

Tumour site	Subsequent therapy distribution						
CRC	**Regorafenib**	**Anti-VEGF + chemotherapy**	**TAS-102**	**Anti-EGFR + chemotherapy**	**FOLFOX**	**FOLFIRI**	**Fluoropyrimidine monotherapy**
	9.68%	35.48%	6.45%	16.13%	6.45%	19.35%	6.45%
Endometrial	**Doxo-rubicin**	**Paclitaxel**	**Megestrol**	**Fulvestrant**	**Tamoxifen**		
	20.00%	20.00%	20.00%	20.00%	20.00%		
Gastric	**FOLFIRI**	**Irinotecan**	**Paclitaxel**	**Ramucirumab + paclitaxel**			
	20.00%	20.00%	20.00%	40.00%			
Small intestine	**Gemcitabine + paclitaxel**	**Ramucirumab + paclitaxel**	**FOLFOX**	**FOLFIRI**			
	20.00%	20.00%	20.00%	40.00%			
Cholangiocarcinoma	**Capecitabine**	**Fluorouracil + irinotecan**	**FOLFOX**				
	50.00%	25.00%	25.00%				

Based on Table 77 of the CS[2]
CRC = colorectal cancer; CS = company submission; EGFR = epidermal growth factor receptor; FOLFIRI = folinic acid, fluorouracil and irinotecan; FOLFOX = folinic acid, fluorouracil and oxaliplatin; IV = intravenous; TAS-102 = tipiracil hydrochloride; VEGF =vascular endothelial growth factor

4.2.9.5 Health state costs

Healthcare resource costs were applied based on health states and tumour site. Healthcare resource use was based on previous NICE TAs for each indication. Costs were sourced from NHS reference costs and the PSSRU. A summary of costs by site and progression can be found in Table 4.9.

Table 4.9: Health state costs by tumour site

Tumour site	HCRU costs by health state (per cycle)	
	Progression-free	**Progressed disease**
CRC	£2.75	£54.00
Endometrial	£73.75	£44.75
Gastric	£211.30	£18.71
Small intestine	£211.30	£18.71
Cholangiocarcinoma	£31.12	£57.16

Based on Table 78 of the CS[2]
CRC = colorectal cancer; CS = company submission; HCRU = health care resource use

4.2.9.6 Adverse event costs

In the company base-case, AE costs were sourced from the NHS Reference costs[35] applied as a one-off at model start for one cycle duration (Table 4.10).

Table 4.10: Adverse event costs per comparator and tumour site

Treatment	Tumour site				
	CRC	Endometrial	Gastric	Small intestine	Cholangiocarcinoma
Pembrolizumab	£59.59	£213.59	£230.83	£151.97	£47.71
Comparator 1	£844.47	£640.30	£527.29	£218.70	£433.19
Comparator 2	£140.76	£640.30	£1,142.40	NA	£557.16

Based on Table 79 of the CS[2]
Comparator 1 = CRC, TAS-102; endometrial, paclitaxel; gastric, paclitaxel; small intestine, nab-paclitaxel; cholangiocarcinoma, mFOLFOX.
Comparator 2 = CRC, pooled FOLFOX/FOLFIRI; endometrial, doxorubicin; gastric, FOLFIRI; small intestine, NA; cholangiocarcinoma, mFOLFIRI.
CRC = colorectal cancer; CS = company submission; FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin: mFOLFIRI = modified folinic acid, fluorouracil, irinotecan; NA = not applicable; TAS-102 = tipiracil hydrochloride

4.2.9.7 Testing cost

In the company's base-case testing costs to identify patients with MSI-H/dMMR were not included. The company conducted a scenario analysis adding testing costs (to all tumour sites but colorectal and endometrial cancer) for patients receiving pembrolizumab in addition to costs for patients with tumours that would test negatively for MSI-H/dMMR biomarkers.

4.2.9.8 End of life costs

End-of life costs were applied to all patients upon death. Different end-of-life costs were applied for each tumour site based on past TAs [38, 39, 40]. The different end-of-life costs are summarised in Table 83 of the CS.

EAG comment: The main concerns of the EAG relate to a) the modelling of subsequent treatments, b) excluding testing costs to identify patients with MSI-H/dMMR from the economic analysis, and c) assuming 100% RDI for most comparators and subsequent treatments.

a) In the company's base-case analysis, patients were modelled to receive subsequent treatments upon progression. The proportion of patients receiving subsequent treatment were estimated based on the KEYNOTE-158 and KEYNOTE-164 trials and were assumed to be equal regardless the initial line of therapy (i.e., pembrolizumab or a comparator treatment). The EAG questions this assumption, as the KEYNOTE trials only included patients that received pembrolizumab, and the company did not provide any further evidence or justification that the proportion of patients receiving subsequent treatments would be the same for the comparators. In addition, the advisory board minutes stated that "[redacted]", [redacted]. Hence, the EAG considers it not unreasonable to assume that the proportion of patients receiving subsequent treatments after pembrolizumab would be higher than the proportion of patients that were treated with a comparator treatment. Next to that, the EAG questions whether the subsequent treatments given in KEYNOTE-158 and KEYNOTE-164 were reflective of subsequent treatments in UK clinical practice. The

KEYNOTE trials did not include patients from the UK, and clinical experts stated during the advisory board that "[redacted]". In addition, the EAG could not find information on subsequent treatment use in KEYNOTE-158, and the observed information in KEYNOTE-164 did not exactly align with the CS. Therefore, the EAG would like to see further justification for assumptions made regarding the modelling of subsequent treatments, in particular concerning (1) the assumption that proportions of patients receiving subsequent treatments are equal regardless of the initial line of therapy (i.e., pembrolizumab or a comparator treatment) and (2) the generalisability of the modelled subsequent treatments to UK clinical practice. The latter should be supported by a comparison of the modelled subsequent treatments to UK clinical guidelines and/or real-world data. In addition, further information on subsequent treatment use in KEYNOTE-158 and KEYNOTE-164 should be provided alongside a description of how this information was used to calculate subsequent treatment use in the economic model.

b) The company did not include testing costs to identify patients with MSI-H/dMMR in their base-case analysis. Experts stated during the advisory board that "[redacted]". The company conducted a scenario analysis including testing costs for gastric cancer, small intestine cancer and cholangiocarcinoma, assuming that testing in colorectal cancer and endometrial cancer is routinely commissioned in the NHS. The company further assumed that 50% of patients per tumour site would already be receiving these tests, as clinicians were unsure of the proportion of patients that would be tested. Although it is unclear to the EAG whether these assumptions are reflective of testing for MSI-H/dMMR in UK clinical practice, the company's scenario analysis was adopted in the EAG base-case.

c) The company derived tumour-site specific pembrolizumab RDI's from the KEYNOTE-158 and KEYNOTE-164 trials (ranging between [redacted]). A scenario analysis was performed assuming a 100% RDI for pembrolizumab, which had a minor impact on the ICER. The company stated that, as for pembrolizumab, RDI for comparators was also considered and, where available, sourced from published literature and respective drug labels. In the economic model, however, a 100% RDI was applied to all comparators except TAS-102 in colorectal cancer (89% RDI). It is unclear to the EAG why a 100% RDI was applied to the comparator treatments and hence further evidence and justification from the company is needed to support this assumption.

4.2.10 Severity

According to the company, patients with previously treated MSI-H/dMMR solid tumours experience a profound worsening in both their expected length of life and their quality of life. The QALY shortfall calculator developed by Schneide 2022 was used to generate absolute and proportional QALY shortfall estimates using the reference case HRQL norms. Patient characteristics used in the analysis were consistent with those informing the base-case economic analysis. There are no previous economic evaluations to provide alternative QALY shortfall estimates in patients with MSI-H/dMMR solid tumours across multiple tumour sites. Within individual tumour sites, for the majority of comparator treatments it was not possible to calculate QALY shortfall based on data reported in previous appraisals as total QALY estimates were redacted (CRC, TA405; endometrial, TA779, ID3811; gastric, TA378; cholangiocarcinoma, TA722).[41-46]

EAG comment: The EAG was able to reproduce the proportional and absolute QALY shortfall provided by the company. Severity may be over- or under-estimated given the lack of evidence in the correct population. The EAG could not get access to the QALY estimates from the TAs mentioned above to further validate the company's estimates. The severity estimates therefore rely only on the company's model and should be interpreted with caution, especially given the limitations to the comparator evidence (not in patients with MSI-H/dMMR and limitations around the selection of comparators) and the approach to estimating QALYs (time-to-death approach may not be appropriate). There is uncertainty around the correct QALY multiplier: for colorectal cancer, the QALY multiplier may [redacted] if the prognosis for patients with MSI-H/dMMR was actually better than that for the comparator population used in the model. However, the company provided a validation of their estimates in colorectal cancer using evidence from patients with MSI-H/dMMR from TA716 and this also suggested a QALY multiplier of [redacted]. For endometrial cancer, according to the absolute QALY shortfall the multiplier would [redacted], and taking into consideration uncertainty about the severity estimates, the multiplier may well fall [redacted]. For gastric cancer, small intestine cancer and cholangiocarcinoma, the EAG notes that the proportional QALY shortfalls are very borderline (absolute QALY shortfall would indicate only [redacted] for gastric and cholangiocarcinoma and [redacted] for small intestine cancer, and proportional QALY shortfall is only just above the threshold to [redacted] for the three tumour sites) and the QALY multiplier may more appropriately be [redacted]. Upon request, the company provided a scenario analysis producing severity estimates using the conventional approach to estimating QALYs based on assigning utilities to the modelled health states rather than based on time-to-death (Table 51 in the clarification response). This resulted in estimates of severity of [redacted] for all tumour sites but cholangiocarcinoma which continued to fall into [redacted] bracket. Given the EAG's concerns about the implementation of the time-to-death approach and the borderline nature of the company's original estimates, the EAG recommends using these QALY multipliers instead and applied these to its base-case.

4.2.11 Uncertainty

The company considers as the key areas of uncertainty:

- Data collected for the individual tumour sites are in some cases from a small number of patients (due to rarity).
- The prognostic value of MSI-H/dMMR is uncertain. Comparator survival outcomes are primarily collected from patients unselected for MSI-H/dMMR, so there may be bias in the comparative estimates.
- Reporting of baseline characteristics in most published studies is poor, making it impossible to adjust for imbalances in possible confounders.
- Long-term survival outcomes with pembrolizumab remain uncertain (due to significant number still at risk at end of follow-up).
- Methodological uncertainty in the capturing of heterogeneity of treatment of tumours in multiple sites.

EAG comment: The EAG agrees broadly with the company's assessment of the key areas of uncertainty. Whilst the company considers that the MSI-H/dMMR status likely predicts worse survival outcomes for patients with metastatic cancer, the EAG still considers this and the impact on treatment effectiveness uncertain. It is therefore not clear to the EAG in what direction the company's analyses are biased.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The CS base-case aggregate probabilistic results indicated that pembrolizumab is both more effective (incremental QALYs of [redacted]) and more costly (addition cost of [redacted]) than SoC, amounting to an ICER of £12,637 per QALY gained and a net health benefit (NHB) of 1.90 QALYs (Table 5.1 below). The CS probabilistic base-case results per indication are shown in Table 5.2 below, with incremental QALYs ranging from [redacted] to [redacted] and incremental costs ranging from [redacted] to [redacted], amounting to ICER ranges of £8,813 and £15,140 per QALY gained and NHB ranging from 1.63 to 2.49 QALYs. All results reflect a QALY weight of 1.2x for the CRC and endometrial sites and 1.7x for gastric, small intestine, cholangiocarcinoma. The probability of pembrolizumab (overall indication) being cost effective at a willingness-to-pay threshold of £30,000 per QALY gained was estimated to be 100% (CS Figure 43).

Table 5.1: Probabilistic CS base-case results - aggregated

Intervention	QALYs	Costs (£)	Incremental QALYs	Incremental Costs	ICER (£/QALY)	NHB (QALYs)
SoC	[redacted]	£34,117	[redacted]	[redacted]	£12,637	1.90
Pembrolizumab	[redacted]	[redacted]				

CS = company submission; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life year; SoC = standard of care

Table 5.2: Probabilistic CS base-case results – per indication

Tumour site	Total QALYs		Total costs		Incremental outcomes			
	Pembro	SoC	Pembro	SoC	ΔQALYs	ΔCosts	ICER	NHB
CRC	[redacted]	[redacted]	[redacted]	£44,214	[redacted]	[redacted]	£8,813	1.91
Endometrial	[redacted]	[redacted]	[redacted]	£25,128	[redacted]	[redacted]	£14,826	1.80
Gastric	[redacted]	[redacted]	[redacted]	£28,924	[redacted]	[redacted]	£14,729	1.63
Small intestine	[redacted]	[redacted]	[redacted]	£35,065	[redacted]	[redacted]	£15,140	2.49
Cholangio-carcinoma	[redacted]	[redacted]	[redacted]	£22,002	[redacted]	[redacted]	£12,196	2.05

CRC = colorectal cancer; CS = company submission; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life year; SoC = standard of care

Overall, the technology is modelled to affect QALYs by:

- Increased PFS for pembrolizumab in the colorectal cancer indication (QALYs in the PF health state increased by [redacted] [redacted] of total QALYs] compared with SoC) and increased time to death in the other indications (QALYs in TTD 360+ days increased by [redacted] [redacted] of total QALYs]).
- Increased OS for pembrolizumab (survival increased by [redacted] years compared with SoC).

Overall, the technology is modelled to affect costs by:

- The higher treatment costs (additional costs of [redacted] compared with SoC).
- The higher resource use costs (additional costs of [redacted] compared with SoC).

EAG comment: The main concern of the EAG relates to the plausibility of the observed PFS (based on a 48 months time horizon) for TAS-102 (colorectal cancer) and mFOLFOX (cholangiocarcinoma) is larger than the modelled PFS based on a lifetime time horizon. This might suggest that PFS for

TAS-102 and mFOLFOX is underestimated and hence the increments versus pembrolizumab potentially overestimated.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

The modelling assumptions that have the greatest effect on the overall indication NHB (based on the company's deterministic sensitivity analyses) were:

- Administration costs of oral chemotherapy
- Proportion of CRC patients receiving subsequent therapy after pembrolizumab.
- Utility values by Grothey 2013[1] to inform HRQoL in CRC.

Based on the company's scenario analyses, modelling assumptions that have the greatest effect on the overall indication NHB were related to:

- Treatment waning
- QALYs and costs discounting
- Survival modelling of OS and PFS in the pembrolizumab arm

EAG comment: The main concern of the EAG relates to the reproducibility of the company's scenario analyses in the economic model. The EAG was unable to reproduce the majority of the scenario analyses reported in Table 93 of the CS. The results of some scenario's (e.g., pembrolizumab OS, PFS – BHM Weibull) also lacked face validity, i.e., the EAG found an increased NHB compared to the company's base-case while the company reported a decreased NHB in CS Table 93. The company should provide further justification for this and step by step details should be provided on how these scenario analyses can be reproduced in the economic model.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The company used expert opinion to guide the modelling approach. An advisory board was conducted to discuss and validate model inputs and assumptions. The advisory board included six clinicians with experience across each of the tumour sites and one health economist.

5.3.2 Technical verification

The company had an independent modeller perform internal validity checks using an internal checklist developed using publicly available checklists such as Drummond and Philips and TECH-VER. Furthermore, the results of the BHM analyses were validated through double programming and visual inspection of the diagnostic, marginal posterior distributions, and model predictions.

5.3.3 Comparisons with other technology appraisals

The company stated that model outcomes were validated against relevant NICE appraisals.

5.3.4 Comparison with external data used to develop the economic model

Model outcomes were validated against literature identified in the SLR and TLRs.

5.3.5 Comparison with external data not used to develop the economic model

The company also attempted to validate model outcomes against external data not used in the economic model. Notably, the company compared survival estimates in their model with those in Thurgar 2021[39], which reported survival data in the US for women with previously treated MSI-H/dMMR unresectable or metastatic endometrial cancer, and Bellone 2022[47] in endometrial cancer as well. In gastric cancer, the company used Lauren et al 2020[48] for external validation. No conclusions were drawn from this exercise.

EAG comment: The main concerns of the EAG relate to:

a) In response to clarification question B29, the company provided a narrative cross validation with the neurotrophin receptor tyrosine kinase (NTRK) appraisals. The company stated that, in contrast to the NTRK submissions, the company did not assume complete homogeneity between tumour sites. The EAG considers this appropriate. The company furthermore highlighted that the NTRK appraisals were tumour-agnostic, which is not the case in this appraisal – and the reason why results were also produced per tumour site. The EAG agrees with this approach.
b) External validation was limited by the lack of external data in the correct population. The company provided a comparison of their PFS and OS estimates for pembrolizumab with evidence from KEYNOTE-061 in patients with gastric cancer. There were only 15 MSI-H patients in a subgroup of this study. The company highlighted that the KEYNOTE-061 OS and PFS were better than in KEYNOTE-158. The company also provided a scenario analysis using these data which improved cost effectiveness, but noted that this should be interpreted with caution because the proportional hazard assumption likely did not hold.
c) The company did perform internal validity checks but unfortunately did not share the results. The EAG did not identify any errors and is satisfied with the internal validity of the model. However, the EAG was unable to reproduce some scenario analysis (see Section 5.2) and this casts doubt over whether validity checks were complete.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm 2020.[49]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide confidence intervals, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/ or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost-effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016)[50]:

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

There were no errors identified by the EAG.

6.1.1.2 Fixing violations

There were no errors identified by the EAG.

6.1.1.3 Matters of judgement

1. Tumour site distribution based on data observed within current UK clinical practice (Section 4.2.6)

The EAG informed tumour site distribution inputs in the economic model based on data observed within UK clinical practice instead of the number of patients included in KEYNOTE-158 and KEYNOTE-164.

2. Utility values for tumour sites from KEYNOTE-158 modelled using a health state by tumour site approach (Section 4.2.8)
   Instead of a time-to-death approach, utility values for tumours sites from KEYNOTE-158 (endometrial, gastric, small intestine, and biliary cancer) were, in line with colorectal cancer, modelled using a tumour site specific utility by health state approach.
3. Inclusion of costs of testing to identify MSH-H/dMMR patients.
   For gastric cancer, small intestine cancer and cholangiocarcinoma, the costs of testing to identify MSH-H/dMMR patients were included.
4. For all tumour sites except cholangiocarcinoma use QALY severity multipliers of [redacted].
   In addition to the colorectal cancer and endometrial cancer tumour sites, QALY severity multiplier of [redacted] were applied to the gastric cancer and small intestine cancer tumour sites. For cholangiocarcinoma, the applied QALY severity multiplier remained [redacted].

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

5. Non-responder analysis for the estimation of the relative effectiveness of pembrolizumab (Section 4.2.6)
   Patients not responding to pembrolizumab treatment in KEYNOTE-158 and KEYNOTE-164 were modelled as a surrogate for comparator OS and PFS outcomes.

6.1.3 EAG subgroup analyses

The EAG provided fully incremental analyses for each individual tumour site.

Table 6.1: Overview of key issues related to the cost effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Aggregating populations across tumour sites based on MSI-H/dMMR status despite unknown MSI-H/dMMR status for most comparators and heterogeneity between tumour sites.	4.2.2	Methods	Further justification, supported by evidence, as to the appropriateness of aggregating results across tumour sites.	+/-	No	Further justification, supported by evidence, as to the appropriateness of aggregating results across tumour sites.
Use of treatment baskets to inform SoC per tumour site which may bias the costs and outcomes of SoC in the economic model.	4.2.4	Methods	The EAG presented the fully incremental analyses results per tumour site.	+/-	Partly	NA
Methodological uncertainty regarding the analysis of relative effectiveness of pembrolizumab	4.2.6	Methods	A non-responder analysis.	+	No	Full NICE DSU TSD 14 and 21 details to support curve choice to extrapolate the non-responder OS and PFS KM data. Further details on the implementation of the non-responder analysis into the economic model, and elaboration on how this analysis also affects the modelled pembrolizumab life years and QALY gains.
Uncertainty regarding the suitability of the BHM approach in the context of this submission.	4.2.6	Methods	Apply BHM approach only to comparable tumour sites, justified and supported by clinical	+/-	No	Apply BHM approach only to comparable tumour sites, justified and supported by clinical arguments and

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
			arguments and evidence rather than statistical arguments. Modelling the KEYNOTE-164 data for the colorectal cancer tumour site separately and applying the BHM approach only to the tumour sites included in the KEYNOTE-158 basket trial. Further elaboration on the suitability of the BHM approach for time-to-event outcomes rather than response outcomes.			evidence rather than statistical arguments. Modelling KEYNOTE-164 data for colorectal cancer separately and applying BHM approach only to tumour sites in the KEYNOTE-158 basket trial. Further elaboration on the suitability of the BHM approach for time-to-event outcomes rather than response outcomes.
Plausibility of time to death approach for modelling HRQoL of tumour sites in KEYNOTE-158.	4.2.8	Methods	Health state-based approach of modelling utilities as a function of progression status.	+	Partly	Full details of the statistical analyses for the various models that were considered.
The EAG questions the assumptions that (1) the proportions of patients receiving subsequent treatments are equal regardless of initial treatment and that (2) the modelled subsequent	4.2.9	Bias and indirectness	Further evidence and justification to support these assumptions.	+/-	No	Further evidence and justification to support these assumptions.

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
treatments are reflective of UK clinical practice.						
The company did not include testing costs to identify patients with MSI-H/dMMR in their base-case analysis.	4.2.9	Methods	Inclusion of cost for MSI-H/dMMR testing.	+	Partly	Evidence to support the assumptions that 1) testing in colorectal cancer and endometrial cancer is routinely commissioned in the NHS, and 2) 50% of patients of the remaining tumour sites already receive these tests.
Uncertainty regarding severity estimates, depending on the chosen approach to estimate HRQoL (time-to-death or health state/progression-based approach).	4.2.10	Methods	Use the health state (progression-) based approach to modelling HRQoL.	+	Partly	QALY estimates from NICE TAs in populations with MSI-H/dMMR status.
Reproducibility and face validity of the majority of the company's scenario analyses.	5.2	Transparency/imprecision	Further justification for lack of reproducibility and face validity. Step by step details on how the company's scenario analyses can be reproduced in the economic model.	+/-	No	Further justification for lack of reproducibility and face validity. Step by step details on how the company's scenario analyses can be reproduced in the economic model.

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator

[b] Explored

BHM = Bayesian hierarchical modelling; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; MSI-H = microsatellite instability-high; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TA = technology appraisal

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously for the overall indication. Results of the fully incremental analyses per tumour site are shown in Tables 6.3 – 6.7. The exploratory scenario analyses, conditional on the EAG base-case, are also presented in these tables. The submitted model file contains technical details on the analyses performed by the EAG (e.g., the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic/probabilistic EAG base-case – overall indication

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
CS base-case						
Pembrolizumab	[redacted]	[redacted]	-	-	-	-
SoC	£33,759	[redacted]	[redacted]	[redacted]	£12,796	1.85
Matter of judgement (1-Tumour site distribution based on UK epidemiological data)						
Pembrolizumab	[redacted]	[redacted]	-	-	-	-
SoC	£32,561	[redacted]	[redacted]	[redacted]	£13,415	1.78
Matter of judgement (2-Health state-based approach to estimate utility values)						
Pembrolizumab	[redacted]	[redacted]	-	-	-	-
SoC	£33,759	[redacted]	[redacted]	[redacted]	£13,744	1.63
Matter of judgement (3-Inclusion of MSH-H/dMMR testing costs)						
Pembrolizumab	[redacted]	[redacted]	-	-	-	-
SoC	£33,759	[redacted]	[redacted]	[redacted]	£12,987	1.83
Matter of judgement (4-1.2 QALY multipliers for tumour sites except cholangiocarcinoma)						
Pembrolizumab	[redacted]	[redacted]	-	-	-	-
SoC	£33,759	[redacted]	[redacted]	[redacted]	£13,974	1.58
Deterministic EAG base-case						
Pembrolizumab	[redacted]	[redacted]	-	-	-	-
SoC	£32,561	[redacted]	[redacted]	[redacted]	£16,856	1.14
Probabilistic EAG base-case						
Pembrolizumab	[redacted]	[redacted]	-	-	-	-
SoC	£33,138	[redacted]	[redacted]	[redacted]	£16,531	1.20
Scenario analysis (5-Non-responder analysis)						
Pembrolizumab	[redacted]	[redacted]	-	-	-	-
SoC	£36,020	[redacted]	[redacted]	[redacted]	£20.336	0.72

[1]iNHB for willingness-to-pay of £30,000 per QALY

CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; MSI-H = microsatellite instability-high; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

Table 6.3: Deterministic EAG base-case – colorectal cancer

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
CS base-case						
Pooled FOLFOX/FOLFIRI	£31,845	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£13,845	1.40
TAS-102	£73,153	[redacted]	[redacted]	[redacted]	Dominated	-1.72

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
None of the matters of judgements impacted the company's base-case results for colorectal cancer.						
Deterministic EAG base-case						
Pooled FOLFOX/FOLFIRI	£31,845	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£13,845	1.40
TAS-102	£73,153	[redacted]	[redacted]	[redacted]	Dominated	-1.72
Scenario analysis (5-Non-responder analysis)						
Pooled FOLFOX/FOLFIRI	£34,326	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,390	0.61
TAS-102	£78,317	[redacted]	[redacted]	[redacted]	Dominated	-1.47

[1]iNHB for willingness-to-pay of £30,000 per QALY

CS = company submission; EAG = Evidence Assessment Group; FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

Table 6.4: Deterministic EAG base-case – endometrial cancer

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
CS base-case						
Doxorubicin	£22,785	[redacted]	-	-	-	-
Paclitaxel	£27,487	[redacted]	[redacted]	[redacted]	Dominated	-0.16
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£15,454	1.73
Matter of judgement (1-Tumour site distribution based on UK epidemiological data) does not impact the company's base-case results for endometrial cancer.						
Matter of judgement (2-Health state-based approach to estimate utility values)						
Doxorubicin	£22,785	[redacted]	-	-	-	-
Paclitaxel	£27,486	[redacted]	[redacted]	[redacted]	Dominated	-0.16
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£17,785	1.26
Matter of judgement (3-Inclusion of MSH-H/dMMR testing costs) does not impact the company's base-case results for endometrial cancer.						
Matter of judgement (4-1.2 QALY multipliers for tumour sites except cholangiocarcinoma) does not impact the company's base-case results for endometrial cancer.						
Deterministic EAG base-case						
Doxorubicin	£22,785	[redacted]	-	-	-	-
Paclitaxel	£27,487	[redacted]	[redacted]	[redacted]	Dominated	-0.16
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£17,785	1.26
Scenario analysis (5-Non-responder analysis)						
Doxorubicin	£30,755	[redacted]	-	-	-	-
Paclitaxel	£36,432	[redacted]	[redacted]	[redacted]	Dominated	-0.19
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,822	0.20

[1]iNHB for willingness-to-pay of £30,000 per QALY

CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; MSI-H = microsatellite instability-high; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

Table 6.5: Deterministic EAG base-case – gastric cancer

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
CS base-case						
FOLFIRI	£24,567	[redacted]	-	-	-	-
Paclitaxel	£29,623	[redacted]	[redacted]	[redacted]	Extendedly Dominated	0.00
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£16,253	1.39
Matter of judgement 1 (Tumour site distribution based on UK epidemiological data) does not impact the company's base-case results for gastric cancer.						
Matter of judgement (2-Health state-based approach to estimate utility values)						
FOLFIRI	£24,567	[redacted]	-	-	-	-
Paclitaxel	£29,623	[redacted]	[redacted]	[redacted]	Extendedly dominated	-0.02
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£18,936	0.96
Matter of judgement (3-Inclusion of MSH-H/dMMR testing costs)						
FOLFIRI	£24,567	[redacted]	-	-	-	-
Paclitaxel	£29,623	[redacted]	[redacted]	[redacted]	Extendedly Dominated	0.00
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£16,593	1.35
Matter of judgement (4-1.2 QALY multipliers for tumour sites except cholangiocarcinoma)						
FOLFIRI	£24,567	[redacted]	-	-	-	-
Paclitaxel	£29,623	[redacted]	[redacted]	[redacted]	Extendedly dominated	-0.05
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,026	0.50
Deterministic EAG base-case						
FOLFIRI	£24,567	[redacted]	-	-	-	-
Paclitaxel	£29,623	[redacted]	[redacted]	[redacted]	Extendedly dominated	-0.06
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£27,387	0.16
Scenario analysis (Non-responder analysis)						
FOLFIRI	£26,668	[redacted]	-	-	-	-
Paclitaxel	£27,515	[redacted]	[redacted]	[redacted]	Dominated	-0.03
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,774	0.40

[1]iNHB for willingness-to-pay of £30,000 per QALY

CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; FOLFIRI = folinic acid, fluorouracil, irinotecan; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; MSI-H = microsatellite instability-high; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

Table 6.6: Deterministic EAG base-case – small intestine cancer

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
CS base-case						
Nab-paclitaxel	£34,793	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£15,054	2.51
Matter of judgement 1 (Tumour site distribution based on UK epidemiological data) does not impact the company's base-case results for small intestine cancer.						
Matter of judgement (2-Health state-based approach to estimate utility values)						
Nab-paclitaxel	£34,793	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£15,514	2.36
Matter of judgement (3-Inclusion of MSH-H/dMMR testing costs)						
Nab-paclitaxel	£34,793	[redacted]	-	-	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£15,370	2.45
Matter of judgement (4-1.2 QALY multipliers for tumour sites except cholangiocarcinoma)						
Nab-paclitaxel	£34,793	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£21,327	1.03
Deterministic EAG base-case						
Nab-paclitaxel	£34,793	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£21,970	0.92
Scenario analysis (Non-responder analysis)						
Nab-paclitaxel	£43,053	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£20,347	1.40

[1]iNHB for willingness-to-pay of £30,000 per QALY

CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; MSI-H = microsatellite instability-high; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

Table 6.7: Deterministic EAG base-case – cholangiocarcinoma

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
CS base-case						
mFOLFIRI	£18,589	[redacted]	-	-	-	-
mFOLFOX	£22,398	[redacted]	[redacted]	[redacted]	Extendedly dominated	-0.07
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£13,164	1.96
Matter of judgement 1 (Tumour site distribution based on UK epidemiological data) does not impact the company's base-case results for cholangiocarcinoma.						
Matter of judgement (2-Health state-based approach to estimate utility values)						
mFOLFIRI	£18,589	[redacted]	-	-	-	-
mFOLFOX	£22,398	[redacted]	[redacted]	[redacted]	Extendedly dominated	-0.08
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£13,962	1.76
Matter of judgement (3-Inclusion of MSH-H/dMMR testing costs)						
mFOLFIRI	£18,589	[redacted]	-	-	-	-
mFOLFOX	£22,398	[redacted]	[redacted]	[redacted]	Extendedly dominated	-0.07
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£14,379	1.82
Matter of judgement 4 (1.2 QALY multipliers for tumour sites except cholangiocarcinoma) does not impact the company's base-case results for cholangiocarcinoma.						
Deterministic EAG base-case						
mFOLFIRI	£18,589	[redacted]	-	-	-	-
mFOLFOX	£22,398	[redacted]	[redacted]	[redacted]	Extendedly dominated	-0.08
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£15,250	1.62
Scenario analysis (Non-responder analysis)						
mFOLFIRI	£20,616	[redacted]	-	-	-	-
mFOLFOX	£24,320	[redacted]	[redacted]	[redacted]	Extendedly dominated	-0.12
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£15,171	1.61

[1]iNHB for willingness-to-pay of £30,000 per QALY

CS = company submission; dMMR = DNA mismatch repair deficient; DNA = deoxyribonucleic acid; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]
benefit; mFOLFIRI = modified folinic acid, fluorouracil, irinotecan; mFOLFOX = modified folinic acid, fluorouracil, oxaliplatin; MSI-H = microsatellite instability-high; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom						

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic) for the overall indication, based on the EAG preferred assumptions highlighted in Section 6.1, was £16,531 per QALY gained. The estimated deterministic base-case ICERs (based on a fully incremental analysis per tumour site) for colorectal cancer, endometrial cancer, gastric cancer, small intestine cancer and cholangiocarcinoma were £13,845, £17,785, £27,387, £21,970, and £15,250 per QALY gained respectively. For the overall indication, the probabilistic EAG base-case analyses indicated a cost effectiveness probability of 100% at a willingness to pay threshold of £30,000 per QALY gained. The most influential adjustments were the 1.2 QALY multipliers for tumour sites except cholangiocarcinoma, and the health state-based approach to estimate utility values. The ICER increased most in the scenario analysis using a non-responder analysis to estimate the relative effectiveness of pembrolizumab.

6.4 Conclusions of the cost effectiveness section

The company's cost effectiveness model complied with the NICE reference case. The most prominent issues highlighted by the EAG are shown in the key issue tables in Section 1.5.

The most important limitation was that the comparator evidence was not specific to MSI-H/dMMR status. Whilst the company argue that their results are therefore conservative, this is uncertain. Second, the comparator was informed by baskets of treatments, which may further under-estimate the effectiveness of SoC. In addition, it was unclear whether results from individual tumour sites should be aggregated given the substantial heterogeneity across tumour sites. Related to this it was unclear whether the company's BHM approach was appropriate. Furthermore, the company's time-to-death approach to model HRQoL of tumour sites informed by KEYNOTE-158 was questionable, as it is not mentioned in the NICE TSD guidance on utilities, seems inconsistent with the chosen model structure and lacks statistical detail and face validity. Resulting from this, there was also uncertainty around the calculated severity estimates per tumour site, as these rely on the approach to estimating QALYs. Next to that, assumptions regarding the modelled proportion of patients receiving subsequent treatments and whether the modelled subsequent treatments were reflective of UK clinical practice was questioned. Another limitation was that the company did not include the costs of testing to identify patients with MSI-H/dMMR in its base-case. Finally, the majority of the company's scenario analyses could not be reproduced and lacked face validity.

The CS base-case ICER (probabilistic) for the overall indication was £12,637 per QALY gained. The estimated EAG base-case ICER (probabilistic) for the overall indication, based on the EAG preferred assumptions highlighted in Section 6.1, was £16,531 per QALY gained. The estimated deterministic base-case ICERs (based on a fully incremental analysis per tumour site) for colorectal cancer, endometrial cancer, gastric cancer, small intestine cancer and cholangiocarcinoma were £13,845, £17,785, £27,387, £21,970, and £15,250 per QALY gained respectively. The most influential adjustments were the 1.2 QALY multipliers for tumour sites except cholangiocarcinoma, and the health state-based approach to estimate utility values. The ICER increased most in the scenario analysis using a non-responder analysis to estimate the relative effectiveness of pembrolizumab.

In conclusion, there is large remaining uncertainty about the effectiveness and cost effectiveness of pembrolizumab, which can be partly resolved by the company by conducting further analyses. This

includes providing an estimation of the OS and PFS relative effectiveness of pembrolizumab in patients that all had a positive MSI-H/dMMR status, an analysis applying the BHM approach only to comparable tumour sites based on clinical arguments and evidence, full details of the statistical analyses for the various time-to-death models that were considered for the estimation of HRQoL, further justification for assumptions made regarding the modelling of subsequent treatments and costs for MSI-H/dMMR testing, and further justification for the lack of reproducibility and face validity of scenario analyses. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of pembrolizumab compared with relevant comparators.

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Single Technology Appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG 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 Friday 31 March 2023** 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 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Minor correction SLR/ITC methodology

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
Section 3.3 states: "No description is given in the CS2 about the specific methodology used to obtain the literature used in the ITC and the matching-adjusted indirect comparison (MAIC)". But this is not the case – it is only the selection of studies from the included list that is not fully explained in the submission (explained in response to CQs)	Adjust wording	Section B.2.1 of CS states (and appendices): "A systematic literature review (SLR) was carried out as per NICE guidance and according to a pre-specified protocol, to identify the clinical evidence relevant to pembrolizumab and any comparator treatments for the indication of interest for this appraisal as described in…"	The word 'obtain' in section 3.3 has been changed to 'select' to clarify that the omission was specifically in terms of the lack of information about the selection of studies for inclusion from the SLR.

Issue 2 Minor adjustment, no literature identified for these smaller sites

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
On p110 it is stated "Although references were cited to show the effect of	Adjust to specify the company could not find adequate evidence for the biliary and small intestine sites.	In section B.1.3.1 we specify that there is a lack of	Not a factual inaccuracy

MSI-H/dMMR on metastatic colorectal cancer (mCRC), endometrial cancer and advanced gastric cancer, no references were given for small intestine or biliary cancer, making this claim impossible to verify.”		literature in small intestine and biliary cancers.	

Issue 3 More context on point about PSMs for comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
Referring to the first bullet point (starting p117) “The company states that the economic analysis is based upon “parametric survival distributions … fitted to the comparator pseudo-IPD with the most clinically plausible extrapolation chosen for use in the base case”. This description is highly ambiguous and unclear. The company has been asked to explain the criteria	The company finds this an odd criticism (and out of line with other sections of the EAG report, 4.2.6 etc, where this is explained better). Severe clarifications are provided below. This issue has been explained in the CS. Four methods are available in the model for deriving comparator PFS and OS: 1) applying an unanchored and unadjusted HR to pembrolizumab curves 2) applying an adjusted MAIC derived HR to pembrolizumab curves 3) fitting independent parametric functions to comparator PFS/OS (with the option to choose from the usual	Current description lacks clarity and will lead to further confusion.	This is not a factual inaccuracy. It is true that the clinical validation is further discussed in Section 4.2.6, but this is completely in line with the criticism that how clinical plausibility was judged is unclear.

for the ‘most clinically plausible extrapolation’. The company failed to respond to this question”	suite of parametric functions) 4) experimental non-responder analysis The comparator efficacy source (whether pooled from disparate data sources or not) is the same across methods 1 to 3. Methods 1 and 2 derived HRs between pembrolizumab curves and the relevant comparator sources and method 3 fits parametric curves to these comparator sources. **These sources by tumour site are explained in response to clarification question A44. The sources described are used for comparator efficacy in methods 1 to 3.** **The comparator source Kaplan-Meier curves (KMs) can be found in the Excel model (OS and PFS tabs, plotted and actual digitised data). This is also the data presented in the ITC/MAIC appendices and as well as included response to clarification question A44.** For method 3, the selection of parametric function is explained in the comparator sections of B.3.3.4 (based on fit statistics, visual fit and clinical		

	opinion). **It is important to note that function choice makes little difference because KM data is so mature for comparators.**		

Issue 4 Minor correction: KN158 is a basket trial

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
On p118 it is stated: "The trial data from pembrolizumab are the single-arm studies KN158 [subgrouped into CRC, gastric, biliary, and small intestine populations] and KN164 [single endometrial population]."	Minor correction: KN164 is the CRC trial	Factual error	This error has been amended.

Issue 5 Pragmatic searches are reported

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
P122: "The company did not provide details of these pragmatic searches therefore the EAG cannot	These details are provided in appendix G (section 3 and 4)	Minor correction	Thank you for drawing our attention to the additional searches for the targeted literature

comment on their suitability.”			review (TLR). You refer to sections 3 & 4 of Appendix G. In both your original submission and the revised document received on 27.1.23 section 4 refers to the reference list and section 3 to details of additional search for NICE TAs. We note that section 2.3 contains details of a targeted literature review (TLR) and presume this is TLR from the 12 August 2022 that you refer to in question A12 of your response to clarification. Unfortunately, as no dates were reported for these searches, we are unable to verify if these are the correct searches. However, we amended our wording to reflect this

Issue 6 Minor issue: specify some evidence is MSI-H

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
P126: “Although, within the economic model, the MSI-H/dMMR status is unknown for patients in the comparator arm.” The sources of comparator efficacy from an MSI-H selected population are explained in the submission (section B.2.9 and B.3.3.3.2): paclitaxel in gastric cancer and paclitaxel/doxorubicin (TPC) in endometrial but other sources are unselected.	This is a minor correction, here and elsewhere in the section (and the report should specify which comparator data sources are MSI-H selected).	Factual inaccuracy.	This error has been amended.

Issue 7 Minor correction: trial names

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
P135: “company modelling the KEYNOTE-158 data for the colorectal cancer	Minor correction: KEYNOTE-164 should read KEYNOTE-158 here (158 is the basket trial) and vice versa	Minor correction about which is basket trial	This error has been amended.

tumour site separately and applying the BHM approach only to the tumour sites included in the KEYNOTE-164 basket trial" Also to be corrected in the Key issues table (Table 6.1 etc)	Elsewhere there is a mention of KEYNOTE-15**7** (which should read **158**)		

Issue 8 For context, KMs are mature and so curve selection irrelevant

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG comments**
P136: "but these details for the comparators are limited to "UK clinical experts validated the selected curves and confirmed that extrapolations were clinically plausible".	For context it would be useful to add that the KM curves for comparator sources are mature and so selection of different functions has minimal impact (i.e. none or tiny extrapolated period and so curves "locked in"), which was explained in the CS and response to CQs.	Further context to aide decision making	Not a factual inaccuracy.

Issue 9 More context, on which shortfall calculation is used based on methods guide

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
On P142/143, the discussion of absolute and proportional shortfall severity weightings should be adjusted slightly to meet the requirements of the new NICE methods guide. In particular, it should specify that the severity calculation that gives the highest severity weighting should be chosen (i.e. in this case it would be proportional rather than absolute shortfall): "6.2.18 The QALY weightings for severity are applied based on absolute and proportional shortfall, whichever implies the greater severity level. If either the proportional or absolute QALY shortfall calculated falls on the cut-	It should be specified that the updated NICE methods guide explicitly identifies the calculation that gives the highest severity modifier should be selected (i.e. in this case proportional over absolute calculations).	Further context to aide decision making	Not a factual inaccuracy. There is no need to re-state preferred methods from the NICE methods guide.

off between severity levels, the higher severity level will apply.”			

Issue 10 EAG report result section has some reporting errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comments
EAG results tables show some reporting errors – EAG should check and correct these reported results.	The results from the EAG base-case seem to have been inputted incorrectly into the tables. It is unclear how they are presented (i.e. the reference treatment should be the comparators so ICERs should be pembrolizumab vs SOC comparator). The pembrolizumab rows have an ICER, perhaps the rows have been confused? Some results also do not match the results from the CEM for the EAG base-case settings. For example, in endometrial neither of the chemotherapies should be dominated by pembrolizumab (their lifetime costs are not higher than pembrolizumab arm costs). The pembrolizumab vs	Correct reporting of modelling results errors to avoid confusion	Not a factual inaccuracy. The EAG reported the fully incremental analyses results per tumour site (as described in section 6.2), rather than pairwise results of pembrolizumab versus comparators. Hence, the least costly comparator is used as the reference treatment.

	paclitaxel ICER in the EAG model is £16,267 (endometrial) but is not reported. Note: to access pairwise results in the "Results tables" sheet pick a tumour site in the drop-down menu on cell I19. Then pick Pairwise from the drop-down menu in cell I23 and then pick the specific comparator in the relevant site (e.g. the drop down menu in cell I28 for endometrial). The Pairwise Results table just below will be updated with the new comparison (just wait a moment for calculations to occur).		

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Single Technology Appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR 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 evaluation, 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.

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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.

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. 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.

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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **23 May 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Technical engagement response form

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About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Merck Sharp & Dohme (MSD) UK Limited**
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

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Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Inappropriate exclusion of comparators from the company decision problem.	No	**It is important to note that pembrolizumab is consistently cost-effective compared with all SOC chemotherapy comparators in all tumour sites, including under exploratory worst-case scenarios (see response to issue 5 and results in Table 2).** **However, the available evidence and clinical opinion suggest that nivolumab and ipilimumab would be the preferred option in clinical practice for patients with metastatic CRC who have been previously treated with chemotherapy, given the superior efficacy of this combination compared to immunotherapy alone. Therefore, MSD accept a restricted recommendation in CRC for this small (and shrinking) group who have not had pembrolizumab previously.** **Irinotecan and raltitrexed, either alone or in combination, are not considered relevant comparators as these are rarely used in clinical practice. This is well-established and supported by clinical expert opinion and previous appraisals.** <u>Nivolumab with ipilimumab (CRC)</u> As per Blueteq, metastatic MSI-H/dMMR colorectal cancer (CRC) patients are not eligible for nivolumab with ipilimumab if they have previously received an anti-PD-1 antibody therapy such as pembrolizumab as first-line treatment. Internal market share estimates suggest that almost [redacted] of metastatic MSI-H/dMMR CRC

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		patients receive pembrolizumab in first line. Chemotherapy is only offered as first-line treatment when the outcome of the MSI-H/dMMR testing is still unknown or where the progression of disease requires a fast response. Nivolumab with ipilimumab represent the second-line treatment of choice for the small subset of metastatic MSI-H/dMMR CRC patients previously treated with chemotherapy and that are suitable for this immunotherapy and CTL-4 combination. The pivotal CheckMate 142 study showed nivolumab and ipilimumab to have far superior efficacy to nivolumab alone (OS and PFS KM curves were > 20% points above nivolumab alone for 6.5 years, see figures below). Pembrolizumab OS/PFS results from KEYNOTE-164 are very similar to those seen for nivolumab in CheckMate 142 and so the combination is superior to immunotherapy alone. Exploratory unanchored MAIC results comparing pembrolizumab with the combination also supported this conclusion: PFS HR of [redacted] and OS HR [redacted]. Clinicians also agreed that the nivolumab and ipilimumab combination is preferred to an immunotherapy alone given the better efficacy achieved when adding a CTLA-4 targeting treatment. Therefore, there is very little (if any) unmet need in this very small patient population that would be met by pembrolizumab. It is possible that some of these patients may have a degree of autoimmune-related comorbidities which make them unsuitable for a dual immunotherapy and CTLA-4 combination. While for these patients nivolumab with ipilimumab is not appropriate (i.e., it is not a relevant comparator), pembrolizumab would be an alternative treatment option, subject to this appraisal. **MSD would accept a recommendation for pembrolizumab in CRC that is restricted to those patients who are unsuitable for treatment with nivolumab and ipilimumab.** CheckMate 142 OS/PFS results comparing nivolumab and ipilimumab (orange) and nivolumab alone (green)

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Figure 2. Progression-free survival

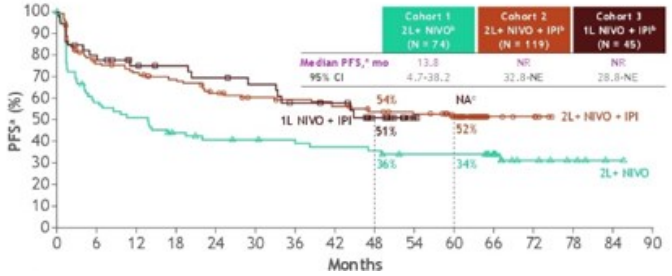
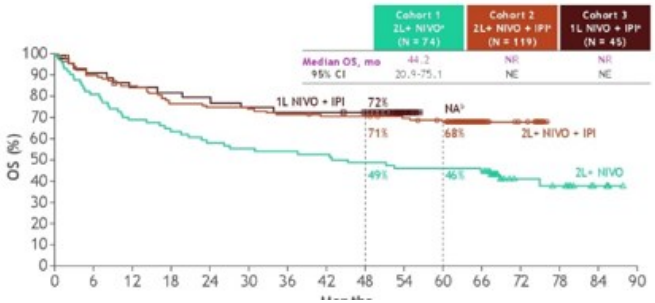


Figure 3. Overall survival



Irinotecan and raltitrexed (CRC)

Irinotecan and raltitrexed, either alone or in combination, are not considered relevant comparators as these are rarely used in clinical practice where 5-fluorouracil and folinic acid-based regimens (one of the relevant comparators in this appraisal for colorectal cancer) are either not tolerated or inappropriate.

This is well-established with the consensus also reached in previous appraisals of technologies in previously treated CRC patients where clinical experts clarified that single-agent irinotecan is rarely used because of the toxicities compared with other options whereas raltitrexed is rarely used in clinical practice for specific populations only, such as for people with a history of heart disease or who develop angina on 5-FU-based chemotherapy (1). Also, when used with other treatments,

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		the dose of irinotecan can be lower and therefore better tolerated than when used as monotherapy (2). Moreover, neither raltitrexed nor irinotecan are indicated as suitable treatments in metastatic colorectal cancer in current NICE guideline (NG151) (3). Raltitrexed and irinotecan have shown similar or lower efficacy compared to other available options, with irinotecan also showing worse toxicity: Raltitrexed • In a randomised controlled trial (RCT) evaluating raltitrexed vs 5-FU+ leucovorin in patients with advanced recurrent metastatic adenocarcinoma of the colon or rectum, there was **no significant difference** between the two groups in overall survival (HR=1.056 [95% CI: 0.847, 1.317]) and time to progression (HR=1.08 [95% CI: 0.889, 1.311]) (4); • In a comparative study of raltitrexed versus a standard 5-FU plus high-dose leucovorin regimen (the Machover regimen) in patients who had advanced recurrent or metastatic adenocarcinoma of the colon or rectum and had not received prior systemic cytotoxic therapy for advanced disease, while the objective tumour response rate was similar in both treatment groups (18.6% of raltitrexed patients vs 18.1% of 5-FU + leucovorin patients), the **median OS favoured the 5-FU + leucovorin** (10.9 months for raltitrexed patients vs 12.3 months for 5-FU + leucovorin patients ; HR=1.15 [95% CI: 0.93, 1.42]); the **median PFS also favoured 5-FU + leucovorin** (3.9 months for raltitrexed patients vs 5.1 months for 5-FU + leucovorin patients; HR=1.33 [95% CI: 1.09 to 1.62]) (5); Irinotecan • In a phase II trial in patients with advanced colorectal cancer previously treated with a fluoropyrimidine and randomly allocated to either single-agent irinotecan or FOLFIRI, there was **no statistically significant difference** between the

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		treatment arms in progression-free survival (HR = 0.81 [95% CI: 0.52, 1.25]; p = 0.34) or overall survival (HR= 0.72 [95% CI: 0.46, 1.12]; p = 0.14) (6); • In a single-arm study in patients with advanced colorectal cancer, single agent irinotecan showed **only modest activity** in patients with prior 5-FU exposure. Of the total 90 patients entered in the previously treated group, 12 (13.3% [95%CI: 7.1, 22.1) experienced a partial response to irinotecan therapy, with a median OS of 8.3 months (range: 0.36 to 34.8). Gastrointestinal and hematologic side effects were reported as the leading toxicities seen with irinotecan (7); • In a non-randomized, open-label phase II clinical trial in patients with mCRC after failure with oxaliplatin and fluoropyrimidine or its derivatives treated with irinotecan and raltitrexed intravenously, the overall response rate was 8.6%, and the disease control rate was 71.4%. The **median PFS was 4.5 month**s (95% CI: 3.8, 5.2) while the **median OS was 12.0 months** (95% CI: 8.5, 15.5) (8). When comparing these results with those for the comparators relevant to this appraisal (pooled FOLFIRI/FOLFOX/FOLFOX4/m-FOLFOX-6 and TAS-102), based on the ITC presented in the submission, similar efficacy (or lower) is consistently observed and therefore the cost-effectiveness analysis would most likely give comparable or more favourable ICERs. <u>Established clinical management (ECM) without pembrolizumab</u> MSD agree with EAG definition of ECM as “a general term for any comparator, provided it is currently used in clinical practice in England and Wales”. In the decision problem table (Table 1 of document B in company submission) as well as in the clarification question responses (response to question B4a), the comparators that are considered to represent the standard of care in the UK in the licensed indications (i.e., the ECM) were listed. These are based on main clinical guidelines and were further validated by clinical experts.

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		As such, the wording “ECM” was replaced with specific comparators that pembrolizumab would replace in clinical practice, subject to this appraisal. This was carried out for each tumour site including small intestine, biliary and gastric cancers. For the treatments indicated by NICE as relevant to the appraisal but that are not considered relevant comparators, a clear justification for their exclusion has been provided above (for nivolumab with ipilimumab, raltitrexed and irinotecan in CRC), in the submission (Table 1 of document B in company submission) and in the clarification questions (responses to questions A18 and B4a). Also, clinical experts when consulted did not identify any other treatments that would represent current practice in the UK. Therefore, we believe that the evidence provided is based on an exhaustive list of treatments that are considered relevant comparators and there are no other treatments being part of the ECM that have been missed.
Issue 2: External validity of the trial evidence to the UK target population.	Yes	**This issue is considered resolved following technical engagement given that no evidence suggesting ethnicity to be a treatment effect modifier is found, and therefore the efficacy outcomes are considered generalisable to the population in the UK.** **The requested subgroup analyses for ethnicity are descriptive and exploratory and, considering that they have been conducted in very small groups of patients, no meaningful conclusions can be drawn about the effectiveness of the technology in these subgroups.** Differences are noted in the proportion of race groups between the trials and the UK cancer incidence data mainly for **colorectal cancer** (67.7% vs 90% White, 26.6% vs 2.1% Asian and 5.6% vs 1.4% Black in KEYNOTE-164 and UK incidence data, respectively) and **gastric cancer** (63% vs 88% White, 28% vs 3.0% Asian and 4% vs 2.7% Black in KEYNOTE-158 and UK incidence data, respectively). In contrast, no substantial differences are observed for the other tumour sites.

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		While the distribution of the baseline characteristics may be affected by the small sample size of the trial population for each tumour site, overall the population in both trials is considered broadly representative of UK patients for the same indications. Moreover, caution should be taken when comparing two different data sources, especially considering that cancer incidence data by ethnicity may fail to capture cancers being diagnosed later in non-White minority ethnic groups so may not reflect the actual incidence. Subgroup analyses by race group are presented in Appendix A below (Table 4Table 9). It should be noted that, due to the very small sample size for some race groups (e.g., 3 and 2 Asian patients in the small intestine and biliary group, respectively), in some cases it was necessary to group multiple race groups into a single subgroup “non-White” to allow less imprecise estimates. These subgroup analyses are descriptive, exploratory, not pre-specified analyses conducted in very small subgroups, and therefore caution should be taken when drawing conclusions about efficacy outcomes in different race groups based on these findings. In particular, the non-White/Other subgroups in most of the tumour sites are very small (2, 5 and 5 participants in biliary, small intestine and gastric cancer, respectively) with the median PFS and OS estimates based on a low number of events, so these results may be due to chance and are not considered informative. No meaningful evidence of differences in ORR between race groups is found in the subgroup analysis in any of the tumour sites, with the ORR 95% CIs mostly overlapping. As anticipated, the very small sample size for non-White patient subgroups in small intestine and biliary cancers resulted in a wider 95% CI. As the subgroups analyses show no evidence suggesting ethnicity to be a treatment effect modifier, the difference in proportions between the trials and UK population is not expected to affect the external validity of the trial results and efficacy outcomes are considered generalisable to the population in the UK.

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Issue 3: Adverse event data for KEYNOTE-158 were aggregated, and not presented for each separate tumour site.	Yes	**This issue is considered resolved following technical engagement. Based on the safety results reported by tumour site, no meaningful differences can be detected in the frequency and type of adverse events across the tumour sites. The AE and AEOSI reported are also generally consistent with the well-known safety profile of pembrolizumab monotherapy.** The safety data were aggregated to increase the sample size and allow more meaningful estimates of adverse event (AE) incidence. The AEs, including adverse events of special interest (AEOSI), reported in the KEYNOTE-158 trial for each tumour site are presented in Table 10Table 18. It should be noted that, due to the small sample size of the tumour site groups, the frequency of AEs, particularly of those that are less common, may not be indicative of the actual incidence of these adverse events in these indications and may be a spurious effect so no clear trend can be detected; therefore, the results should be interpreted with caution. With regard to the more common AEs, the frequency and type of adverse events did not vary substantially across the tumour sites, with diarrhoea, fatigue, vomiting, abdominal pain, arthralgia and pruritus being consistently reported within same range of frequency [redacted] in all tumour sites. These adverse events are also reported as very common AEs associated with pembrolizumab monotherapy in the Summary of Product Characteristics (SmPC). The majority of the other AEs reported with an incidence ≥5% in each tumour site are also presented as very common or common in the SmPC. The proportion of participants with Grade ≥ 3 AEs ranged from [redacted] to [redacted] across all tumour sites, with few Grade ≥ 3 AEs being reported with a frequency greater than 5%. Hypothyroidism and hyperthyroidism were the most frequently reported AEOSI (≥3 participants) across all tumour sites (except for biliary and small intestine cancers where no AEOSI was reported for more than 2 participants). These are also generally consistent with the well-known safety profile of pembrolizumab monotherapy.

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		Overall, these safety results from the KEYNOTE-158 trial demonstrate that pembrolizumab is well tolerated in participants with dMMR or MSI-H tumours across the four tumour sites.
Issue 4: Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population.	Yes	**dMMR/MSI-H is considered a relevant predictive biomarker of response to pembrolizumab in the five tumour types relevant to this appraisal. This is supported by evidence from a number of studies stratified by MSI status that is suggestive of the increased activity of pembrolizumab in MSI-H patients relative to non MSI-H cancers.** **dMMR/MSI-H patients are not expected to respond better to chemotherapy than pMMR/MSS patients (i.e., MSI status is likely to be a negative prognostic factor) and therefore it is unlikely the ICERs would be higher (but may be potentially lower) if comparisons were performed in the dMMR/MSI-H comparator population.** For the five tumour types relevant to this appraisal, dMMR/MSI-H is considered a relevant predictive biomarker of response to pembrolizumab. This is supported by opinion of clinical experts who emphasised the role of **MSI-H as treatment effect modifier in relation to treatment with checkpoint inhibitors like pembrolizumab in these tumour sites**. (9) Previous studies had found that there was a dramatic overexpression of immune checkpoint-related proteins in the microenvironment of MSI CRC tumours, suggesting that immunotherapeutic interventions involving checkpoint blockade might be selectively effective in this subset of cancers. (10) This is also supported by a number of studies that include MSI-H patients and allow a within-study visual comparison of efficacy outcomes between MSI-H and non-MSI-H subgroups.

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		• In the KEYNOTE-061 study, an RCT comparing pembrolizumab with paclitaxel in participants with advanced gastric /gastroesophageal junction adenocarcinoma that progressed after therapy with platinum and fluoropyrimidine, MSI-H gastric cancer patients treated with pembrolizumab had longer PFS and OS compared to chemotherapy; (11) also, a visual comparison of efficacy evidence between the MSI-H and non-MSI-H subgroups is suggestive of the increased activity of pembrolizumab in MSI-H advanced gastric cancer patients relative to non MSI-H cancer patients (median PFS of 17.8 vs 1.5 months and median OS not being reached vs 6.5 months in MSI-H and non-MSI-H subgroups, respectively) (Table 19 and Figure 1Figure 2). While the small number of patients in the MSI-H group may limit the interpretation of the findings, the baseline characteristics of the two subgroups are overall comparable (Table 20). • The ZEBRA study, a Phase 2 multicentre study of pembrolizumab in 40 patients with previously treated small-bowel adenocarcinoma, offers additional support for the predictive value of MSI-H. (12) The study was not biomarker-restricted but did stratify by MSI-H. The non-MSI-H participants had an ORR of only 8% with median PFS of 2.8 months and median OS of 6.6 months; in contrast, the ORR in MSI-H participants was 50% with median PFS and OS not being reached, though based on only 4 participants (Table 21). This is consistent with the ORR of 55.0% observed in the KEYNOTE-158 trial and highlights the significant activity of pembrolizumab in MSI-H small intestine tumours. • In the KEYNOTE-158 trial, 104 non-MSI-H patients with advanced biliary cancer treated with pembrolizumab within a different cohort had an ORR of 5.8% (2.1- 12.1) as opposed to 40.9% (20.7, 63.6) for MSI-H biliary cancer patients in cohort K (the cohort relevant to this appraisal). (13) Also, PFS and OS were shorter than in MSI-H patients (median PFS of 4.2 vs 2.0 months and median OS 19.4 vs 7.4 months in MSI-H and non-MSI-H cohorts, respectively)

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		(Table 22). This represents further evidence of the positive predictive value of the MSI status for the approved indications. In addition to the evidence provided in the company submission about the prognostic value of MSI status, further evidence from the systematic literature review (SLR) suggests that **dMMR/MSI-H patients that are treated with chemotherapy are likely to have worse (or at least similar) prognosis than pMMR/MSS patients**. • In the KEYNOTE-775 trial, the evidence source used in the MAIC for the relevant comparators in endometrial cancer (paclitaxel or doxorubicin), randomisation was stratified according to MMR status. (14) While ORR and PFS are overall similar in dMMR and pMMR chemotherapy participants, OS findings suggest worse survival outcomes for dMMR patients with a median OS of 8.6 (5.5 – 12.9) for the dMMR subgroup vs 12.0 (10.8 – 13.3) for pMMR participants (Table 24); at 12 months, OS rate for the dMMR subgroup was 39.1% while nearly 50% of pMMR participants were still alive at 12 months (Figure 3Figure 4). Baseline characteristics of the two subgroups are presented in Table 25. • In addition to KEYNOTE-775, the SLR conducted for endometrial cancer identified McMeekin 2015 in which the comparator was paclitaxel or doxorubicin. This study was a Phase III randomized trial evaluating second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer with at least one failed prior platinum-based chemotherapeutic regimen. (15) Median age in the paclitaxel or doxorubicin group was 64 (33-88), similarly to dMMR population in KEYNOTE-775 (63.0) and the majority of patients were White whereas no baseline data were reported about ECOG PS and number of prior lines of therapy, which limit the comparison between the two groups. While the MSI/MMR status in the study population is unknown (i.e., unselected population), response and survival outcomes for the paclitaxel or doxorubicin group in the McMeekin 2015 study show better results compared to the dMMR chemotherapy population in

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		KEYNOTE-775 (ORR 15.7% vs 12%; median OS 12.3 [10.7–15.4] vs 8.6 [5.5 – 12.9]) (Table 26). In contrast, the results in the paclitaxel or doxorubicin group in the McMeekin 2015 study are similar to all patients group in KEYNOTE-775 (Table 26). • In KEYNOTE-061 (gastric cancer), a naïve comparison of efficacy outcomes between MSI-H and non-MSI-H paclitaxel subgroups suggests similar prognosis (Table 19). Based on the above, it is reasonable to assume that ICERs would most likely not be higher if comparisons were performed in the MSI-H/dMMR comparator population. While acknowledging the limitations of the evidence above (e.g., lack of formal statistical comparison), this evidence certainly highlights a continued unmet need based on the clinical outcomes observed for the current standard of care in patients with MSI-H/dMMR cancers for these tumour types. This unmet need could be addressed with the availability of a more effective treatment such as pembrolizumab.
Issue 5: High risk of bias in comparative efficacy.	Yes	**Relative effectiveness is not particularly biased compared to other later line solid-tumour indications and results remain highly cost-effective under alternative approaches, extreme treatment waning and exploratory worst-case extrapolation scenarios.** The relative treatment comparisons are potentially biased to the extent that both KEYNOTE-164 and KEYNOTE-158 are single-arm trials, but this is not uncommon in solid tumour indications. In addition, comparator source OS/PFS KM (Kaplan–Meier) curves are fully mature which reduces uncertainty (i.e., virtually all patients are dead in the observed period).

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		As acknowledged by the EAG, relative treatment effects were explored in the company submission via naïve ITCs, MAICs (where possible) and fitting independent parametric models (PSMs) to comparator evidence sources. The latter was selected in the base-case based on the violation of proportional hazards assumption; however, results remain cost-effective under all approaches. The EAG adopt the non-responder analyses for exploratory purposes (with curve selection based on best fits), which use pembrolizumab non-responders to reflect comparator efficacy. It should be noted that this is a conservative approach given that it involves fitting PSMs to data for patients from KEYNOTE-158 and KEYNOTE-164 who did not respond to 2L+ treatment with pembrolizumab (i.e., did not achieve complete or partial response). These will tend to be worst-case patients in a 3L+ setting who do not fit the license population. It is true that they are some subsets of the trial dataset used to model pembrolizumab efficacy and so there will be some control for confounders (i.e. within study or before and after type analysis); but this is only the case for time-constant and not time-variant factors (e.g. comorbidity status, change in fitness, new line of treatment). However, MSD agree this can be a useful worst-case exploratory scenario. **Under EAG settings (which reflect significant waning) and extreme exploratory worst-case scenarios all pairwise comparisons, weighted within tumour site results and overall indication results remain cost-effective (see Table 2 in sensitivity analysis results below):** • Extreme treatment effect waning: waning from 7 to 9 years (from start of treatment) was included in the company base-case but also carried over to the EAG base-case and as explained previously the impact of this is considered clinically implausible but was included to reflect how cost-effective pembrolizumab remains: o Plotted hazard functions for pembrolizumab over the duration of the trials (> 5 years) showed no evidence of treatment waning as patients

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		finish pembrolizumab treatment (in-line with previous pembrolizumab trials). ○ The plots below show that particularly for the 3 smaller sites (gastric, small intestine, biliary) there is an unrealistic drop in survival projections, which is highly conservative and inconsistent with clinical opinion. ○ Waning is counter-intuitive in this case given that virtually all patients are dead in the chemotherapy comparators we wane against and this may explain the irregular impact on pembrolizumab survival. • Scenario A: shows non-responder analysis for comparators (in line with EAG exploratory analysis) as a worst-case scenario. • Scenario B: BHM (Bayesian hierarchical model) curve selections and PSM comparator curve selections that give the worst ICERs. ○ These selections minimise (maximise) overall and progression-free state accrued QALYs for pembrolizumab (comparators). Comparator PSM selections do not drive results given the maturity of KMs. The Gompertz is now the BHM selection for all pembrolizumab OS/PFS curves, which was rejected by clinicians as too pessimistic (and does not have the best fit statistics). • Scenario C: This is the same as B but now the piecewise BHM for PFS is selected, this tends to have a better visual fit as discussed in the response to clarification questions. ○ Both standard parametric survival models (PSMs) and BHM models did not fit the initial drop in PFS well. The drop is likely related to the first on-study imaging time point being performed at 9 weeks in both KEYNOTE-164 and KEYNOTE-158. • Scenario E: This scenario employs standard PSMs for pembrolizumab (based on a balance of fit statistics and previous clinical validations as explained in the response to clarification); these give improved ICERs compared to scenarios A to C.

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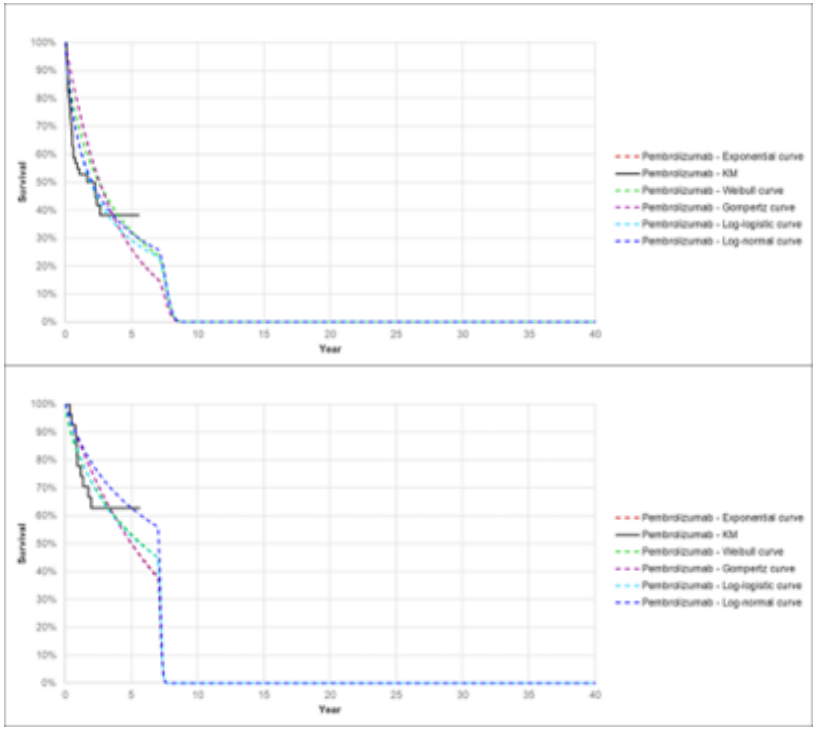
		Extreme impact of treatment waning on pembrolizumab survival (Gastric and small intestine sites) 
Issue 6: Populations were aggregated across all tumour sites based on their MSI-H/dMMR status. However, MSI-H/dMMR status for most comparators was unknown and	No	**This issue is considered resolved following technical engagement, given that pembrolizumab is consistently cost-effectiveness in all individual pairwise comparisons (and so by definition cost-effective in all aggregated results).**

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heterogeneity between tumour sites seems substantial.		The cost-effectiveness of pembrolizumab vs. each individual chemotherapy comparator in any tumour site is accessible in the model and presented in the results and scenarios below. "Aggregation" here refers to the weighted averaging of these individual pairwise lifetime model outputs (total costs, total QALYs and ICERs) to produce cost-effectiveness results by tumour site and further to this for the overall indication. The weightings for aggregating comparator results within a tumour site were based on clinician estimates of market share; the aggregating of these further into overall indication results were based on either tumour site proportions from the trial or epidemiological calculations. Results are cost-effective for all pairwise comparisons and so by definition all aggregated results indicate cost-effectiveness – weighting calculations therefore are not a key technical issue that determines cost-effectiveness. Additionally, there is remarkable similarity in outcomes across the traditional chemotherapy comparators in all tumour sites: virtually all patients are dead by 4 years and accrued lifetime QALYs are consistently around 1. Lifetime accrued costs are also remarkably similar across chemotherapy comparators. This is different to assumptions about the heterogeneity of pembrolizumab efficacy between tumour sites and how different methods for extrapolating pembrolizumab OS/PFS make different assumptions about heterogeneity (issue 9).
Issue 7: Treatment baskets were used to inform standard of care per tumour site, which may bias the costs and outcomes of standard of care in the economic model.	No	**This issue is considered resolved following technical engagement and has no significant impact on cost-effectiveness.** To clarify, there are no baskets of costed treatments but final model lifetime cost-effectiveness results (e.g. lifetime accrued costs, QALYs, ICERs) for each pairwise comparison and these are aggregated as described above.

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		When multiple sources of OS/PFS data for a given comparator (in a given tumour site) were identified these KM curves were usually pooled. For example, the abundance of source studies for 2L+ FOLFIRI/FOLFOX in CRC was a challenge; in this case different combinations of sources were compared side-by-side in the response to clarification questions and it was clear that efficacy did not vary significantly. MSD is indifferent about presenting results fully incrementally; however, for ease of interpretation results below are presented in pairwise fashion (pembrolizumab vs comparator).
Issue 8: The selection of patients in the comparator studies was not based on their MSI-H/dMMR status, which introduced (methodological) uncertainty in the estimation of the relative effectiveness of pembrolizumab.	Yes	**The lack of available chemotherapy comparator data from sources that select patients based on dMMR/MSI-H status is unlikely to have a significant impact on cost-effectiveness and may even produce conservative cost-effectiveness results.** dMMR/MSI-H selected sources were only available for the paclitaxel in Gastric and TPC (paclitaxel/doxorubicin) in endometrial pairwise comparisons. Available evidence suggests that dMMR/MSI-H status is potentially a negative prognostic factor (see response to issue 4 above) and so results for chemotherapies with evidence from unselected sources may be slightly too optimistic (and ICERs higher than they otherwise would be). As explained in the technical engagement call, there is no error in the non-responder analysis; pembrolizumab arm results change with comparator curve fittings in any analysis when the waning functionality is on. In exploratory scenario analyses that can be considered the best case for chemotherapy comparators and worst case for pembrolizumab, results show

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		consistent cost-effectiveness. See response to issue 5 above and the exploratory scenario results below (Table 2).
Issue 9: The suitability of the Bayesian hierarchical model approach in the context of this submission was questionable.	Yes	**The "true" ICERs are somewhere around the BHM approach (assumes neither complete heterogeneity or homogeneity in pembrolizumab efficacy between tumour sites) and standard parametric models (PSMs) that assume complete heterogeneity. Pembrolizumab is consistently cost-effective across all approaches, extreme waning, and worst-case scenarios which limits the impact of uncertainty arising from this issue.** A method that pooled all pembrolizumab PFS/OS data irrespective of tumour site and so assumed complete homogeneity between all 5 tumour sites in KEYNOTE-164 (CRC) and KEYNOTE-158 (endometrial, gastric, small intestine, biliary) was never presented. Instead a Bayesian hierarchical model (BHM) and standard PSM approach was used to extrapolate the 5+ years of KM data: • BHMs: This is a multilevel model that assumes some exchangeability in efficacy between tumour sites, the greater the differences in PFS/OS between sites the greater the exchangeability. ○ This is a middle ground between assuming complete homogeneity in pembrolizumab efficacy between sites (naive pooling) and complete heterogeneity (fitting separate PSM models as though sites are independent trials). ○ This is the first appraisal where the BHM is used directly on survival outcomes; due to data limitations the NTRK tumour agnostic appraisals used the BHM applied only to response outcomes (then used these to weight survival curves). ○ The model used was that suggested by the York EAG in the NTRK appraisals. The rate/scale/location parameter of a given survival distribution is a function of tumour site level random effects that vary by tumour site membership (as well as other standard fixed effects).

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		• PSMs: These are the standard parametric models used in most oncology appraisals and in this context assume perfect heterogeneity in pembrolizumab efficacy across tumour sites (i.e., all tumour sites are assumed independent trials with no modelled MSI-H class effect). In the BHM approach, the model is fit across all five tumour sites (i.e., including the CRC dataset from KEYNOTE-164). The EAG make the defensible point that it is inappropriate to include CRC in the BHM model given that it is a separate trial. However, a case can be made that it is reasonable to the extent that if CRC was included as a site in KEYNOTE-158, results would not differ systematically from results in KEYNOTE-164. This may be the case given that both trials are included in the same license: trial protocols are very similar, inclusion/exclusion criteria consistent, and sample size calculations suggest that a CRC site in KEYNOTE-158 would have a comparable sample size to KEYNOTE-164 (i.e., sample sizes are broadly proportional to incidence of the tumour type). Additional BHM models are time consuming to run and so as a compromise scenario the current BHM is applied to the four KEYNOTE-158 sites, with a standard PSM being applied to the CRC site. This makes very little difference to results as expected (Table 2; scenario D). As already explained in response to issue 5, even under worst-case scenarios pembrolizumab remains cost-effective (Table 2) which should limit uncertainty arising from this technical issue.
Issue 10: The time-to-death utility approach to model the health-related quality of life of tumour sites included in KEYNOTE-158 was questionable.	No	**Pembrolizumab remains highly cost-effective under both the original time-to-death (TTD) and health state (HS) utility approaches for the KEYNOTE-158 sites, with HS now reflected in the updated base-case. However, the severity modifier is sensitive to this setting and all three smaller sites achieve the highest modifier weight under TTD (1.7) which makes pembrolizumab even more cost-effective.**

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		KEYNOTE-164 (CRC) did not collect HRQoL data and so HS utilities are applied from the most conservative literature source (as agreed by the EAG). A TTD approach estimates utility weights based on the time from death category a patient falls into; in contrast to a HS approach that applies progression-free and progressed utilities. For the KEYNOTE-158 tumour sites (endometrial, gastric, small intestine, biliary) a TTD utility model was fitted to the whole sample (irrespective of tumour site status) given the small numbers of patients by tumour site in some TTD categories. The HS utility approach for KEYNOTE-158 was fitted to produce different utilities by tumour site. When presented with the methods, clinicians believed both were clinically plausible but there was a slight preference for TTD given that for immunotherapies there is a longer tail of survival irrespective of progression status (i.e., time from death can matter more than progression status). Very conservatively, the comparator chemotherapies in these KEYNOTE-158 sites are given these same pembrolizumab utilities in modelling. Under either approach pembrolizumab remains cost-effective – however the TTD utility approach gives lower ICERs and lower accrued QALYs for chemotherapy comparators and tips the gastric and small intestine sites into the highest severity modifier category: • Endometrial: under TTD the ICER is lower compared with HS (£15,126 vs £17,408). Severity modifier remains at 1.2. • Gastric: under TTD the ICER is lower compared with HS (£22,736 vs £26,548). Severity modifier also increases to 1.7, lowering the ICER further to £16,049. • Small intestine: under TTD the ICER is lower compared with HS (£21,774 vs £22,440). Severity modifier also increases to 1.7, lowering the ICER further to £15,370.

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		• Biliary: under TTD the ICER is lower compared with HS (£13,657 vs £14,471). Severity modifier remains at 1.7.
Issue 11: Assumptions regarding the modelling of subsequent treatments were questionable.	No	**This issue is considered resolved following technical engagement and has no significant impact on cost-effectiveness, because as expected most patients receive BSC at 3L+ in these metastatic cancers.** Subsequent treatment proportions from the KEYNOTE-164 and KEYNOTE-158 trials show that most patients will not receive subsequent treatments but BSC. Depending on tumour site the proportion varies from 60-80% receiving BSC. The proportions receiving subsequent treatments are as follows: 26.6% (CRC), 22.9% (endometrial), 19.6% (gastric), 40.7% (small intestine) and 33.3% (biliary). These high proportions on BSC are expected in the later line metastatic setting and clinicians broadly agreed with these proportions. For simplicity, it was assumed that comparator treatment arms in the model also received these same proportions and same treatments, and this was supported by clinicians. Accrued life-time subsequent treatment costs vary slightly between pembrolizumab and comparator arms due to differences in progression rates. The reported subsequent treatments are composed of traditional chemotherapies and it is unclear how they might differ in practice between pembrolizumab and the comparators. For example, it is unlikely that patients in the comparator arms receive immunotherapies in these later lines but if they did this would reduce ICERs slightly (i.e., higher accrued subsequent treatment costs for comparators). Scenarios that double proportions of subsequent treatments or remove them entirely have been added to the model (bottom of Model Control sheet), but as expected these change the ICERs by around 1%.
Issue 12: Testing costs to identify patients with MSI-H/dMMR were not included in	No	**This issue is considered resolved following technical engagement and has no significant impact on cost-effectiveness. There is some consensus that dMMR/MSI-H testing is uncertain and less well established in the smaller**

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the company's base-case analysis.		**tumour sites (gastric, small intestine, biliary) and so 50% testing costs are assumed. Results remain cost-effective even when 100% testing costs are included in modelling.** There is a broad consensus that testing is established in the larger tumour sites (CRC, endometrial) based on clinician input and previous appraisals and so no additional testing costs are included in the model for these. The MSI-H test directory (UK genomics hubs) officially cover all five tumour sites in the full license related to this appraisal (16). However, in clinical practice there is uncertainty about how established testing is for the three smaller sites (gastric, small intestine, biliary). As a compromise, 50% of testing costs are included in the updated base-case (Table 1). 100% testing costs are included in a scenario analysis, but this has little impact and pembrolizumab remains cost-effective in these sites (Table 3).
Issue 13: Severity estimates were based on the company's modelling of QALYs, which was subject to limitations, and therefore uncertain.	No	**The EAG preference for severity modifiers is reflected in the updated base-case (all sites achieve a 1.2 multiplier, with biliary achieving the 1.7). However, it is important to emphasise that under plausible settings the gastric and small intestine sites achieve the highest 1.7 multiplier and this should be considered in decision making**. For all sites the comparator/SOC proportional QALY shortfall is well into the cut-offs for achieving at least a 1.2 severity modifier with updated base-case settings (>85%): [redacted] (CRC),[redacted] (endometrial),[redacted] (gastric),[redacted] (small intestine) and [redacted] (biliary). There is agreement that the biliary site achieves the 1.7 modifier (proportional QALY shortfall is >95%), however it is important to emphasise how easy it is to tip the gastric and small intestine sites into this higher category. If you reduce accrued

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		lifetime QALYs for the comparators in these sites by only 0.08 (i.e. 8% of a QALY) the highest severity modifier is achieved. There are several reasons why the model may overestimate accrued QALYs for these chemotherapy comparators and so in reality gastric and small intestine may reach the cut-off for the highest severity modifier: • The modifiers are sensitive to the TTD vs. HS utility settings and under the TTD approach the gastric and small intestine sites achieve the 1.7 multiplier (see issue 10 above). • For the KEYNOTE-158 sites (all sites excluding CRC) the chemotherapy comparators are given pembrolizumab KEYNOTE-158 derived utilities and this will overestimate accrued QALYs for these comparators (especially in the progression free state as QoL is likely to be lower on chemotherapies). • MSI-H/dMMR status is potentially a negative prognostic factor for patients receiving these chemotherapies (see response to issue 4) and so for unselected comparator sources we may be overestimating survival and accrued QALYs (all comparators in CRC, small intestine and biliary and FOLFIRI in gastric).
Issue 14: The majority of the company's scenario analyses could not be reproduced and lacked face validity.	Yes	**This issue is considered resolved following technical engagement and has no significant impact on cost-effectiveness.** MSD apologise that some scenario results in the company submission contained errors because of a typo in named ranges in the VBA code for the automated scenario functionality. This has been corrected (switch added at the bottom of Model Controls sheet) with automated scenario analyses results re-run in the updated model. The correction makes very little difference to scenario analysis results. In addition, MSD has corrected an error in the way administration costs were applied to oral therapies in the model – the HRG cost was applied per

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		administration instead of as a one-off cost as appropriate. This has been corrected and for simplicity all oral admin costs are £0 now (see bottom of Model Controls sheet). This mainly impacts the TAS-102 comparison in CRC (the only oral administration comparator) and ICERs remain well below threshold levels.

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Summary of changes to the company's cost-effectiveness estimate(s)

Table 1 is the updated base-case and is the same as the EAG base-case. Results are presented as pembrolizumab vs. comparator and are inclusive of pembrolizumab confidential PAS. Probabilistic ICERs are very similar (overall indication PSA ICER is £18,240). Key settings are as follows:

- The error for oral medication dosing is corrected (and oral admin costs set to £0) and this mainly impacts the TAS-102 (CRC) comparison (see response to issue 14 above)
- These include the QALY severity weightings endorsed by the EAG: 1.2 multiplier in all sites except biliary (1.7 multiplier)
- Health state (by site) utility approach instead of time-to-death utilities
- 50% testing costs are included for the 3 smaller tumour sites: gastric, endometrial, and biliary
- Using epidemiological calculations as the basis of tumour site weighting when deriving overall indication ICER

Table 1 Updated company base-case (EAG base-case inclusive of extreme treatment effect waning from company base-case)

		Pairwise ICERs	Weighted tumour site ICER
Overall indication deterministic ICER:		£18,549	
Colorectal	TAS-102	£13,413	£13,783
	Pooled FOLFOX/FOLFIRI	£13,962	
Endometrial	Paclitaxel	£16,395	£17,408
	Doxorubicin	£17,914	
Gastric	Paclitaxel	£26,166	£26,548
	FOLFIRI	£27,387	

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Small intenstine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£22,440	£22,440
Biliary (cholangiocarcinoma)	mFOLFOX	£14,374	£14,471
	mFOLFIRI	£15,330	

Sensitivity analyses around revised base case

The results below reflect EAG settings as described above but with additional exploratory worst-case settings (see response to issue 5 above). Note that B is pre-programmed into the scenario selection functionality on the Model Controls sheet; scenario C is the same as B but PFS selections are then switched to piecewise BHM models (same functions); and D is the "naive PSM" scenario in scenario selection (but EAG settings and waning must be re-inputted again).

Table 2 EAG base-case but with additional exploratory and extreme worst-case scenario results

			Pairwise ICERs	**Weighted tumour site ICER**
A: Pembrolizumab Non-responder analysis	**Overall indication ICER:**		£22,382	
	Colorectal	TAS-102	£20,978	£19,981
		Pooled FOLFOX/FOLFIRI	£19,554	
	Endometrial	Paclitaxel	£24,080	£26,053
		Doxorubicin	£27,040	
	Gastric	Paclitaxel	£24,774	£24,662
		FOLFIRI	£24,402	
	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£20,347	£20,347
	Biliary (cholangiocarcinoma)	mFOLFOX	£14,136	£14,250
		mFOLFIRI	£15,271	
	Overall indication ICER:		£22,879	

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B: Worst case (pessimistic) pembrolizumab curve selections and best case (optimistic) comparator selections	**Colorectal**	TAS-102	£17,811	£18,536
		Pooled FOLFOX/FOLFIRI	£18,892	
	Endometrial	Paclitaxel	£20,016	£24,366
		Doxorubicin	£27,160	
	Gastric	Paclitaxel	£26,887	£27,408
		FOLFIRI	£28,642	
	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£25,168	£25,168
	Biliary (cholangiocarcinoma)	mFOLFOX	£15,368	£15,507
		mFOLFIRI	£16,777	
C: analysis B but with worst case piecewise for pembrolizumab PFS	**Overall indication ICER:**		£22,912	
	Colorectal	TAS-102	£16,653	£17,243
		Pooled FOLFOX/FOLFIRI	£17,531	
	Endometrial	Paclitaxel	£20,081	£24,345
		Doxorubicin	£27,069	
	Gastric	Paclitaxel	£28,176	£28,698
		FOLFIRI	£29,935	
	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£26,547	£26,547
	Biliary (cholangiocarcinoma)	mFOLFOX	£14,893	£15,029
		mFOLFIRI	£16,268	
D: PSM for pembrolizumab in CRC; remaining sites BHM	**Overall indication ICER:**		£18,553	
	Colorectal	TAS-102	£13,354	£13,724
		Pooled FOLFOX/FOLFIRI	£13,904	
	Endometrial	Paclitaxel	£16,395	£17,408
		Doxorubicin	£17,914	
	Gastric	Paclitaxel	£26,166	£26,548
		FOLFIRI	£27,387	

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	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£22,440	£22,440
	Biliary (cholangiocarcinoma)	mFOLFOX	£14,374	£14,471
		mFOLFIRI	£15,330	
E: PSMs for pembrolizumab (best fit and clinically plausible)	**Overall indication ICER:**		£19,143	
	Colorectal	TAS-102	£13,354	£13,724
		Pooled FOLFOX/FOLFIRI	£13,904	
	Endometrial	Paclitaxel	£15,913	£16,871
		Doxorubicin	£17,350	
	Gastric	Paclitaxel	£28,138	£28,508
		FOLFIRI	£29,316	
	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£25,908	£25,908
	Biliary (cholangiocarcinoma)	mFOLFOX	£17,005	£17,117
		mFOLFIRI	£18,109	

Table 3 EAG base-case but with 100% testing costs accrued in gastric, small intestine and biliary

		Pairwise ICERs	**Weighted tumour site ICER**
Overall indication ICER:		£18,803	
Colorectal	TAS-102	£13,413	£13,783
	Pooled FOLFOX/FOLFIRI	£13,962	
Endometrial	Paclitaxel	£16,395	£17,408
	Doxorubicin	£17,914	
Gastric	Paclitaxel	£26,761	£27,133
	FOLFIRI	£27,948	
Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£22,902	£22,902

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Biliary (cholangiocarcinoma)	mFOLFOX	£15,680	£15,775
	mFOLFIRI	£16,618	

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APPENDIX A

Issue 2

KEYNOTE-164 (CRC)

Table 4 ORR by race group based on IRC Assessment per RECIST 1.1 (ASaT Population) (KEYNOTE-164, CRC)

		Objective Response (CR+PR)
	n	% (95% CI†)
All	42	33.9 (25.6; 42.9)
White	27	[redacted]
Non-White	15	[redacted]
Asian	11	[redacted]
Only confirmed responses are included (n=42) † Based on binomial exact confidence interval method. Database Cutoff Date: 19FEB2021		

Abbreviations: ASaT, all subjects as treated population; CR, complete response; PR, partial response
Notes: Non-White subgroup includes Asian (n=11) and Black Or African American (n=4)

Table 5 Summary of Progression-Free Survival (PFS) Based on IRC Assessment per RECIST 1.1 (ASaT Population) (KEYNOTE-164, CRC)

	White	**Non-White**	**Asian**
Subjects in population	84	40	33

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Number (%) of PFS Events	[redacted]	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]	[redacted]
Median PFS (Months)§	[redacted]	[redacted]	[redacted]
95% CI for Median PFS§	[redacted]	[redacted]	[redacted]
PFS rate at 6 Months in % §	[redacted]	[redacted]	[redacted]
PFS rate at 12 Months in % §	[redacted]	[redacted]	[redacted]
PFS rate at 24 Months in % §	[redacted]	[redacted]	[redacted]
PFS rate at 36 Months in % §	[redacted]	[redacted]	[redacted]
Progression-free survival is defined as time from first day of study treatment to disease progression, or death, whichever occurs first. § From product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 19FEB2021			

Abbreviations: ASaT, all subjects as treated population; PFS, progression-free survival
Notes: Non-White subgroup includes Asian (n=33) and Black Or African American (n=7)

Table 6 Summary of Overall Survival (ASaT Population) (KEYNOTE-164, CRC)

	White	Non-White	Asian
Subjects in population	84	40	33
Number (%) of Events	[redacted]	[redacted]	[redacted]

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Person-Months	[redacted]	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]	[redacted]
Median OS (Months)§	[redacted]	[redacted]	[redacted]
95% CI for Median OS§	[redacted]	[redacted]	[redacted]
OS rate at 12 Months in % §	[redacted]	[redacted]	[redacted]
OS rate at 24 Months in % §	[redacted]	[redacted]	[redacted]
OS rate at 36 Months in % §	[redacted]	[redacted]	[redacted]
OS rate at 48 Months in % §	[redacted]	[redacted]	[redacted]
§ From product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 19FEB2021			

Abbreviations: ASaT, all subjects as treated population; OS, overall survival
Notes: Non-white subgroup includes Asian (n=33) and Black Or African American (n=7)

KEYNOTE-158

Objective Response rate (ORR)

Table 7 Summary of Best Objective Response Based on RECIST1.1 per Central Radiology Assessment (ASaT Population in Cohort K)

Gastric cancer

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Response Evaluation	White (N=32)			Asian (N=14)			Other (N=5)		
	n	%	95% CI[a]	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)	[redacted]								
Partial Response (PR)									
Objective Response (CR+PR)									
Stable Disease (SD)									
Progressive Disease (PD)									
Non-evaluable (NE)									
No Assessment									

Endometrial cancer

Response Evaluation	White (N=70)			Non-White (N=11)		
	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)	[redacted]					
Partial Response (PR)						
Objective Response (CR+PR)						
Stable Disease (SD)						

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Progressive Disease (PD)	[redacted]					
Non-evaluable (NE)	[redacted]					
No Assessment	[redacted]					
Participants with missing race are not included.						

Biliary cancer

Response Evaluation	White (N=20)			Non-White (N=2)		
	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)	[redacted]					
Partial Response (PR)	[redacted]					
Objective Response (CR+PR)	[redacted]					
Stable Disease (SD)	[redacted]					
Progressive Disease (PD)	[redacted]					
No Assessment	[redacted]					

Small Intestine Cancer

Response Evaluation	White (N=22)			Non-White (N=5)		
	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)	[redacted]					
Partial Response (PR)	[redacted]					
Objective Response (CR+PR)	[redacted]					

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Stable Disease (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease (PD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Assessment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Based on binomial exact confidence interval method.
Notes: Central radiology assessed responses per RECIST 1.1 (confirmed) are included in this table.
'No Assessment' (NA) counts subjects who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.
Database Cutoff Date: 12JAN2022

Progression-free Survival (PFS)

Table 8 Summary of Progression-Free Survival (PFS) Based on RECIST 1.1 per Central Radiology Assessment (ASaT Population in Cohort K)

Gastric Cancer

	White (N=32)	Asian (N=14)	Other (N=5)
Number (%) of PFS Events	[redacted]	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]	[redacted]
Median PFS (Months)[a]	[redacted]	[redacted]	[redacted]
95% CI for Median PFS[a]	[redacted]	[redacted]	[redacted]
PFS rate at 6 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 12 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 24 Months in % [a]	[redacted]	[redacted]	[redacted]

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PFS rate at 36 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 48 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 60 Months in % [a]	[redacted]	[redacted]	[redacted]

Endometrial Cancer

	White (N=70)	Non-White (N=11)
Number (%) of PFS Events	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]
Median PFS (Months)[a]	[redacted]	[redacted]
95% CI for Median PFS[a]	[redacted]	[redacted]
PFS rate at 6 Months in % [a]	[redacted]	[redacted]
PFS rate at 12 Months in % [a]	[redacted]	[redacted]
PFS rate at 24 Months in % [a]	[redacted]	[redacted]
PFS rate at 36 Months in % [a]	[redacted]	[redacted]
PFS rate at 48 Months in % [a]	[redacted]	[redacted]
PFS rate at 60 Months in % [a]	[redacted]	[redacted]
Participants with missing race are not included.		

Biliary Cancer

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	White (N=20)	Non-White (N=2)
Number (%) of PFS Events	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]
Median PFS (Months)[a]	[redacted]	[redacted]
95% CI for Median PFS[a]	[redacted]	[redacted]
PFS rate at 6 Months in % [a]	[redacted]	[redacted]
PFS rate at 12 Months in % [a]	[redacted]	[redacted]
PFS rate at 24 Months in % [a]	[redacted]	[redacted]
PFS rate at 36 Months in % [a]	[redacted]	[redacted]
PFS rate at 48 Months in % [a]	[redacted]	[redacted]
PFS rate at 60 Months in % [a]	[redacted]	[redacted]

Small Intestine Cancer

	White (N=22)	Non-White (N=5)
Number (%) of PFS Events	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]
Median PFS (Months)[a]	[redacted]	[redacted]
95% CI for Median PFS[a]	[redacted]	[redacted]
PFS rate at 6 Months in % [a]	[redacted]	[redacted]
PFS rate at 12 Months in % [a]	[redacted]	[redacted]
PFS rate at 24 Months in % [a]	[redacted]	[redacted]
PFS rate at 36 Months in % [a]	[redacted]	[redacted]
PFS rate at 48 Months in % [a]	[redacted]	[redacted]
PFS rate at 60 Months in % [a]	[redacted]	[redacted]

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[a] From product-limit (Kaplan-Meier) method for censored data.
Notes: Progression-free survival is defined as time from date of first dose to disease progression, or death, whichever occurs first.
Abbreviations: NR, Not reached; PFS, progression-free survival
Database Cutoff Date: 12JAN2022

Overall Survival (OS)

Table 9 Summary of Overall Survival (ASaT Population in Cohort K)

Gastric Cancer

	White (N=32)	Asian (N=14)	Other (N=5)
Death (%)	[redacted]	[redacted]	[redacted]
Median Survival (Months)[a]	[redacted]	[redacted]	[redacted]
95% CI for Median Survival[a]	[redacted]	[redacted]	[redacted]
OS rate at 6 Months in % [a]	[redacted]	[redacted]	[redacted]
OS rate at 12 Months in % [a]	[redacted]	[redacted]	[redacted]
OS rate at 24 Months in % [a]	[redacted]	[redacted]	[redacted]
OS rate at 36 Months in % [a]	[redacted]	[redacted]	[redacted]
OS rate at 48 Months in % [a]	[redacted]	[redacted]	[redacted]
OS rate at 60 Months in % [a]	[redacted]	[redacted]	[redacted]
OS rate at 72 Months in % [a]	[redacted]	[redacted]	[redacted]

Endometrial Cancer

	White	Non-White

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	(N=70)	(N=11)
Death (%)	[redacted]	[redacted]
Median Survival (Months)[a]	[redacted]	[redacted]
95% CI for Median Survival[a]	[redacted]	[redacted]
OS rate at 6 Months in % [a]	[redacted]	[redacted]
OS rate at 12 Months in % [a]	[redacted]	[redacted]
OS rate at 24 Months in % [a]	[redacted]	[redacted]
OS rate at 36 Months in % [a]	[redacted]	[redacted]
OS rate at 48 Months in % [a]	[redacted]	[redacted]
OS rate at 60 Months in % [a]	[redacted]	[redacted]
OS rate at 72 Months in % [a]	[redacted]	[redacted]
Participants with missing race are not included		

Biliary Cancer

	White (N=20)	Non-White (N=2)
Death (%)	[redacted]	[redacted]
Median Survival (Months)[a]	[redacted]	[redacted]
95% CI for Median Survival[a]	[redacted]	[redacted]
OS rate at 6 Months in % [a]	[redacted]	[redacted]
OS rate at 12 Months in % [a]	[redacted]	[redacted]
OS rate at 24 Months in % [a]	[redacted]	[redacted]
OS rate at 36 Months in % [a]	[redacted]	[redacted]
OS rate at 48 Months in % [a]	[redacted]	[redacted]
OS rate at 60 Months in % [a]	[redacted]	[redacted]
OS rate at 72 Months in % [a]	[redacted]	[redacted]

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Small Intestine Cancer

	White (N=22)	Non-White (N=5)
Death (%)	[redacted]	[redacted]
Median Survival (Months)[a]	[redacted]	[redacted]
95% CI for Median Survival[a]	[redacted]	[redacted]
OS rate at 6 Months in % [a]	[redacted]	[redacted]
OS rate at 12 Months in % [a]	[redacted]	[redacted]
OS rate at 24 Months in % [a]	[redacted]	[redacted]
OS rate at 36 Months in % [a]	[redacted]	[redacted]
OS rate at 48 Months in % [a]	[redacted]	[redacted]
OS rate at 60 Months in % [a]	[redacted]	[redacted]
OS rate at 72 Months in % [a]	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.
Abbreviations: NR, Not reached; OS, overall survival
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Issue 3

Table 10 Adverse Event Summary - Participants: MSI-H with Gastric, Endometrial, Biliary and Small Intestine Cancer (ASaT Population)

	Gastric		Endometrial		Biliary (cholangiocarcinoma)		Small intestine	
	Pembrolizumab 200 mg Q3W							
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	51		83		22		27	
with one or more adverse events	[redacted]							
with drug-related[a] adverse events	[redacted]							
with serious adverse events	[redacted]							
with serious drug-related adverse events	[redacted]							
with dose reduction due to an adverse event	[redacted]							
with dose reduction due to a drug-related adverse event	[redacted]							
who died	[redacted]							
who died due to a drug-related adverse event	[redacted]							
discontinued drug due to an adverse event	[redacted]							
discontinued drug due to a drug-related adverse event	[redacted]							

[a] Determined by the investigator to be related to the drug
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
Database Cutoff Date: 12JAN2022

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Gastric cancer

The most frequently reported AEs (incidence ≥20%) were diarrhoea, asthenia, fatigue, and arthralgia. Anaemia, abdominal pain, alanine transferase increased, and pruritus were reported with a frequency of 19.6%.

Table 11 Frequency and severity of adverse events according to the SOC classification- Participants: MSI-H with Gastric Cancer (All grade AE with Incidence ≥5% or Grade 3+ AE with Incidence ≥5%) (ASaT Population)

SOC rating/event	Pembrolizumab 200 mg Q3W n (%)		n (%)	
	Toxicity of all Grades		Toxicity of Grade ≥ 3	
Participants in population	51		51	
with one or more adverse events	[redacted]		[redacted]	
with no adverse events				
Blood and lymphatic system disorders				
Anaemia				
Cardiac disorders				
Ear and labyrinth disorders				
Endocrine disorders				
Hypothyroidism				
Eye disorders				
Gastrointestinal disorders				
Diarrhoea				
Abdominal pain				
Constipation				
Vomiting				
Abdominal pain upper				
Nausea				
Ascites				
General disorders and administration site conditions				
Asthenia	[redacted]		[redacted]	
Fatigue				
Pyrexia				
Influenza like illness				
Malaise				
Oedema peripheral				

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Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations				
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Investigations				
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders				
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders				
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders				
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders				
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03 and MedDRA version is 24.1
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Table 12 Participants With Adverse Events by AEOSI Category and Preferred Term (Incidence > 0%) - Participants: MSI-H with Gastric Cancer (ASaT Population)

	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	51	
with one or more adverse events	[redacted]	[redacted]
with no adverse events		
Colitis		
Colitis		
Guillain-Barre Syndrome		
Guillain-Barre syndrome		
Hepatitis		
Hepatitis		
Hyperthyroidism		
Hyperthyroidism		
Hypothyroidism		
Hypothyroidism		
Myocarditis		
Myocarditis		
Myositis		
Myopathy		
Nephritis		
Nephritis		
Tubulointerstitial nephritis		
Pneumonitis		
Interstitial lung disease		
Pneumonitis		

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
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Endometrial cancer

The most frequently reported AEs (incidence ≥20%) were diarrhoea, nausea, vomiting, fatigue, arthralgia, pruritus, urinary tract infection and decreased appetite.

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Table 13 Frequency and severity of adverse events according to the SOC classification - Participants: MSI-H with Endometrial Cancer (All grade AE with Incidence ≥5% or Grade 3+ AE with Incidence ≥5%) (ASaT Population)

SOC rating/event	Pembrolizumab 200mg Q3W n (%) Toxicity of all Grades		Pembrolizumab 200mg Q3W n (%) Toxicity of Grade ≥ 3	
Participants in population	83		83	
with one or more adverse events	[redacted]		[redacted]	
with no adverse events	[redacted]		[redacted]	
Blood and lymphatic system disorders	[redacted]		[redacted]	
Anaemia	[redacted]		[redacted]	
Lymphopenia	[redacted]		[redacted]	
Endocrine disorders	[redacted]		[redacted]	
Hypothyroidism	[redacted]		[redacted]	
Hyperthyroidism	[redacted]		[redacted]	
Eye disorders	[redacted]		[redacted]	
Gastrointestinal disorders	[redacted]		[redacted]	
Diarrhoea	[redacted]		[redacted]	
Nausea	[redacted]		[redacted]	
Vomiting	[redacted]		[redacted]	
Constipation	[redacted]		[redacted]	
Abdominal pain	[redacted]		[redacted]	
Dry mouth	[redacted]		[redacted]	
General disorders and administration site conditions	[redacted]		[redacted]	
Fatigue	[redacted]		[redacted]	
Asthenia	[redacted]		[redacted]	
Pyrexia	[redacted]		[redacted]	
Oedema peripheral	[redacted]		[redacted]	
Infections and infestations	[redacted]		[redacted]	
Urinary tract infection	[redacted]		[redacted]	
Upper respiratory tract infection	[redacted]		[redacted]	
Nasopharyngitis	[redacted]		[redacted]	
Injury, poisoning and procedural complications	[redacted]		[redacted]	
Investigations	[redacted]		[redacted]	
Aspartate aminotransferase increased	[redacted]		[redacted]	
Blood creatinine increased	[redacted]		[redacted]	
Alanine aminotransferase increased	[redacted]		[redacted]	
Lymphocyte count decreased	[redacted]		[redacted]	
Weight decreased	[redacted]		[redacted]	

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Metabolism and nutrition disorders				
Decreased appetite				
Hypomagnesaemia				
Hyperglycaemia				
Musculoskeletal and connective tissue disorders				
Arthralgia				
Back pain				
Muscle spasms				
Myalgia				
Pain in extremity				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Nervous system disorders				
Headache				
Dizziness				
Neuropathy peripheral				
Psychiatric disorders				
Insomnia				
Anxiety				
Renal and urinary disorders				
Reproductive system and breast disorders				
Vaginal haemorrhage				
Respiratory, thoracic and mediastinal disorders				
Cough				
Dyspnoea				
Nasal congestion				
Skin and subcutaneous tissue disorders				
Pruritus				
Rash				
Rash maculo-papular				
Vascular disorders				
Hypertension				

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03 and MedDRA version is 24.1
Database Cutoff Date: 12JAN2022

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Table 14 Participants With Adverse Events by AEOSI Category and Preferred Term (Incidence > 0%) - Participants: MSI-H with Endometrial Cancer (ASaT Population)

	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	83	
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Enterocolitis	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Infusion Reactions	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Myositis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Severe Skin Reactions	[redacted]	[redacted]
Pemphigoid	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Type 1 Diabetes Mellitus	[redacted]	[redacted]
Type 1 diabetes mellitus	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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: 12JAN2022

Biliary cancer (Cholangiocarcinoma)

The most frequently reported AEs (incidence ≥20%, corresponding to approximately ≥4 study participants) were diarrhoea, abdominal pain, vomiting, constipation, fatigue, pyrexia, asthenia, alanine transferase increased, blood alkaline phosphatase increased and weight decreased.

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Table 15 Frequency and severity of adverse events according to the SOC classification - Participants: MSI-H with Cholangiocarcinoma (All grade AE with Incidence ≥5% or Grade 3+ AE with Incidence ≥5%) (ASaT Population)

SOC rating/event	Pembrolizumab 200mg Q3W n (%) Toxicity of all Grades		n (%) Toxicity of Grade ≥ 3	
Participants in population	22		22	
with one or more adverse events	[redacted]		[redacted]	
with no adverse events	[redacted]		[redacted]	
Blood and lymphatic system disorders	[redacted]		[redacted]	
Anaemia	[redacted]		[redacted]	
Cardiac disorders	[redacted]		[redacted]	
Eye disorders	[redacted]		[redacted]	
Gastrointestinal disorders	[redacted]		[redacted]	
Diarrhoea	[redacted]		[redacted]	
Abdominal pain upper	[redacted]		[redacted]	
Vomiting	[redacted]		[redacted]	
Constipation	[redacted]		[redacted]	
Nausea	[redacted]		[redacted]	
Dyspepsia	[redacted]		[redacted]	
General disorders and administration site conditions	[redacted]		[redacted]	
Fatigue	[redacted]		[redacted]	
Pyrexia	[redacted]		[redacted]	
Asthenia	[redacted]		[redacted]	
Oedema peripheral	[redacted]		[redacted]	
Non-cardiac chest pain	[redacted]		[redacted]	
Hepatobiliary disorders	[redacted]		[redacted]	
Infections and infestations	[redacted]		[redacted]	
Nasopharyngitis	[redacted]		[redacted]	
Influenza	[redacted]		[redacted]	
Liver abscess	[redacted]		[redacted]	
Sepsis	[redacted]		[redacted]	
Urinary tract infection	[redacted]		[redacted]	
Vascular device infection	[redacted]		[redacted]	
Injury, poisoning and procedural complications	[redacted]		[redacted]	
Rib fracture	[redacted]		[redacted]	
Investigations	[redacted]		[redacted]	
Alanine aminotransferase increased	[redacted]		[redacted]	

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Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased				
Aspartate aminotransferase increased				
Blood bilirubin increased				
Platelet count decreased				
Metabolism and nutrition disorders				
Decreased appetite				
Musculoskeletal and connective tissue disorders				
Arthralgia				
Back pain				
Muscle spasms				
Nervous system disorders				
Headache				
Psychiatric disorders				
Insomnia				
Respiratory, thoracic and mediastinal disorders				
Cough				
Epistaxis				
Skin and subcutaneous tissue disorders				
Rash				
Pruritus				
Rash maculo-papular				

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03 and MedDRA version is 24.1
Database Cutoff Date: 12JAN2022

Table 16 Participants With Adverse Events by AEOSI Category and Preferred Term (Incidence > 0%) - Participants: MSI-H with Cholangiocarcinoma (ASaT Population)

	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	22	
with one or more adverse events	[redacted]	[redacted]
with no adverse events		
Hepatitis		
Hepatitis		
Hypothyroidism		

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Hypothyroidism	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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: 12JAN2022

Small Intestine Cancer

The most frequently reported AEs (incidence ≥20%, corresponding to approximately ≥5 study participants) were diarrhoea, abdominal pain, fatigue and pruritus.

Table 17 Frequency and severity of adverse events according to the SOC classification - Participants: MSI-H with Small Intestine Cancer (All grade AE with Incidence ≥5% or Grade 3+ AE with Incidence ≥5%) (ASaT Population)

SOC rating/event	Pembrolizumab 200mg Q3W n (%) Toxicity of all Grades	Pembrolizumab 200mg Q3W n (%) Toxicity of Grade ≥ 3
Participants in population	27	27
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]

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Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions				
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia				
Pyrexia				
Influenza like illness				
Oedema peripheral				
Hepatobiliary disorders				
Hepatitis				
Infections and infestations				
Influenza				
Upper respiratory tract infection				
Conjunctivitis				
Nasopharyngitis				
Tooth infection				
Investigations				
Alanine aminotransferase increased				
Aspartate aminotransferase increased				
Blood alkaline phosphatase increased				
Metabolism and nutrition disorders				
Decreased appetite				
Dehydration				
Musculoskeletal and connective tissue disorders				
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain				
Myalgia				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache				
Dizziness				
Psychiatric disorders				
Depression				
Insomnia				
Renal and urinary disorders				
Reproductive system and breast disorders				
Respiratory, thoracic and mediastinal disorders				

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Cough	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea				
Skin and subcutaneous tissue disorders				
Pruritus				
Rash				
Vascular disorders				
Hot flush				

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03 and MedDRA version is 24.1
Database Cutoff Date: 12JAN2022

Table 18 Participants With Adverse Events by AEOSI Category and Preferred Term (Incidence > 0%) - Participants: MSI-H with Small Intestine Cancer (ASaT Population)

	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	27	
with one or more adverse events	[redacted]	[redacted]
with no adverse events		
Colitis		
Colitis		
Hepatitis		
Hepatitis		
Hyperthyroidism		
Hyperthyroidism		
Hypothyroidism		
Hypothyroidism		
Pancreatitis		
Pancreatitis		
Pneumonitis		
Interstitial lung disease		
Pneumonitis		

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
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Issue 4

Table 19 KEYNOTE-061 (gastric) – efficacy outcomes in pembrolizumab and paclitaxel groups (MSI-H and non-MSI-H subgroups)

	Pembrolizumab			Paclitaxel		
	MSI-H subgroup, n=15	**Non-MSI-H* subgroup, n=281**	**All patients, n=296**	**MSI-H subgroup, n=12**	**Non-MSI-H* subgroup, n=284**	**All patients, n=296**
ORR, % (95% CI)	46.7 (21.3 – 73.4)	9.3 (6.2 – 13.3)	11.1 (7.8 – 15.3)	16.7 (2.1 – 48.4)	12.3 (8.7 – 16.7)	12.5 (9.0- 16.8)
DOR, median (range), months	NR (5.5. – 26.0)	Not available	18.0 (1.4 – 26.0)	NR (2.2 – 12.2)	Not available	5.5 (1.3 – 17.7)
Median PFS (95% CI), months	17.8 (2.7 – NR)	1.5 (1.4 – 1.6)	1.5 (1.4 – 1.6)	3.5 (2.0 – 9.8)	4.1 (3.2 – 4.2)	4.1 (3.2-4.2)
Median OS (95% CI), months	NR (5.6 – NR)	6.5 (5.0 – 8.6)	6.7 (5.4 – 8.9)	8.1 (2.0 – 16.7)	8.3 (7.6-8.9)	8.3 (7.7- 8.8)
OS rate, % (95% CI), 12 months	73 (44-89)	32.0 (26.7 – 37.5)	34 (29 – 39)	25 (6-50)	28.3 (23.3- 33.6)	28 (23-33)
OS rate, % (95% CI), 24 months	59 (31 – 79)	Not available	18 (13 – 23)	Not available	Not available	9 (6-13)

*non-MSI-H status includes patients not evaluable for MSI-H
Abbreviations: DOR, duration of response; MSI-H, microsatellite high; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival
Notes: Median (range) follow-up: 7.9 (0.2-27.7) months
Source: Chao et al. 2021 (11)

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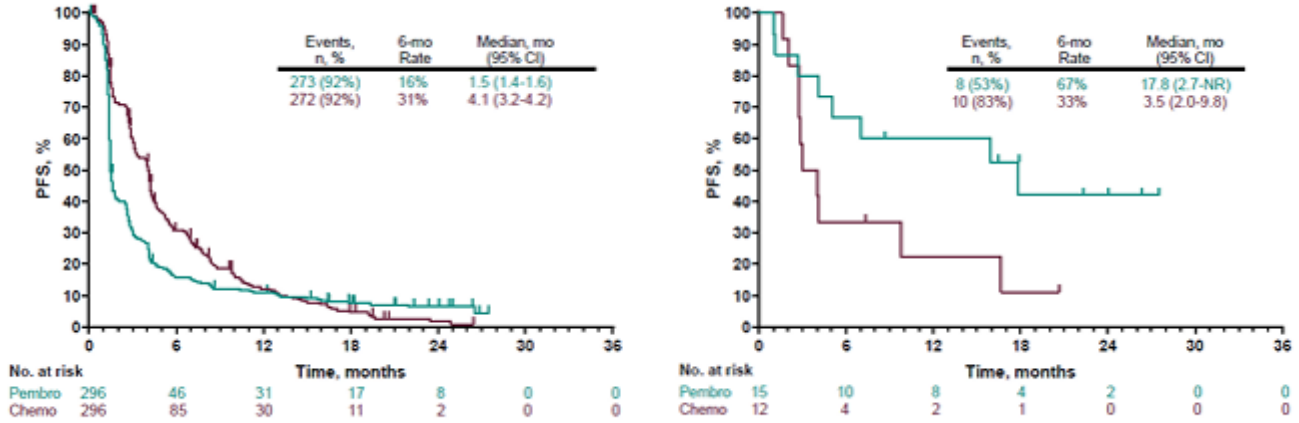
Figure 1 Kaplan-Meier estimates of PFS in patients with advanced gastric cancer (KEYNOTE-061); all patients (left), patients with MSI-H tumours (right)



Source: Chao et al. 2021 (11)

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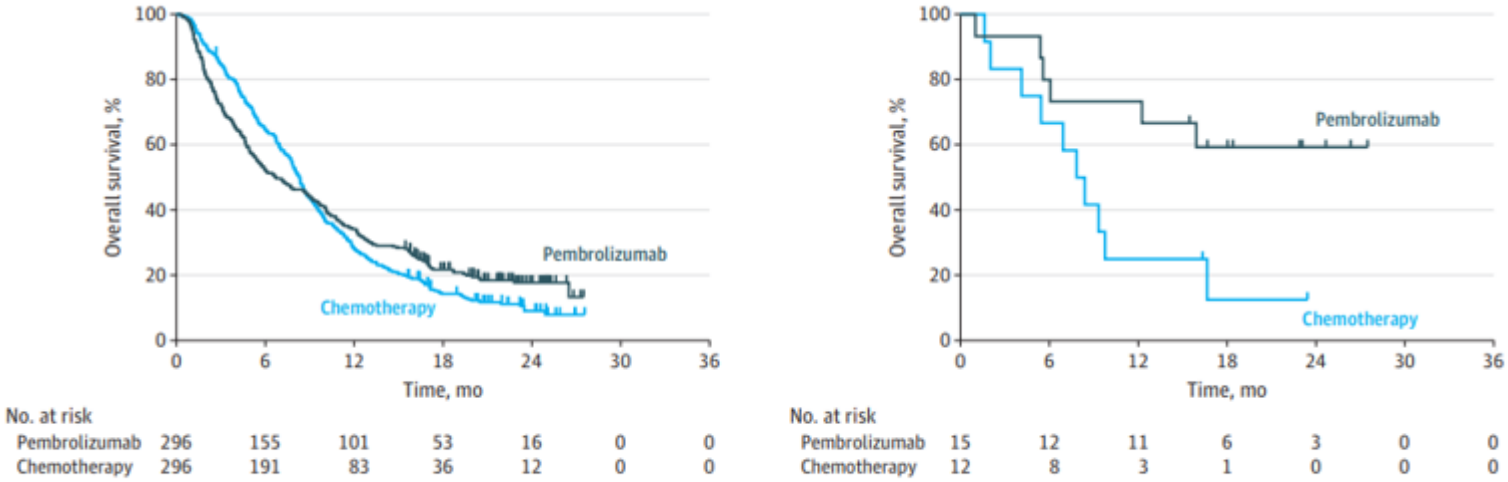
Figure 2 Kaplan-Meier estimates of OS in patients with advanced gastric cancer (KEYNOTE-061); all patients (left), patients with MSI-H tumours (right)



Source: Chao et al. 2021 (11)

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Table 20 Baseline characteristics of patients with advanced gastric cancer (KEYNOTE-061)

	KEYNOTE-061, MSI-H, n=27		KEYNOTE-061, non-MSI-H or MSI-H non-evaluable, n=565	
	Pembrolizumab, n=15	Paclitaxel, n=12	Pembrolizumab, n = 281	Paclitaxel, n=284
Age, median (range), years	67 (36-76)	63 (43-75)	62 (27-87)	60.0 (20-86)
Male	7 (46.7)	8 (66.7)	195 (69)	200 (70)
Australia/Europe/ North America	10 (66.7)	7 (58.3)	180 (64)	180 (63)
Asia	4 (26.7)	3 (25.0)	84 (30)	86 (30)
Rest of World	1 (6.7)	2 (16.7)	17 (6)	18 (6)
ECOG PS 0	5 (33.3)	4 (33.3)	122 (43)	133 (47)
ECOG PS 1	10 (66.7)	8 (66.7)	159 (57)	150 (53)
Metastatic disease	14 (93.3)	11 (91.7)	278 (99)	283 (100)
Stomach	11 (73.3)	10 (83.3)	196 (70)	190 (67)
Gastroesophageal junction adenocarcinoma	4 (26.7)	2 (16.7)	85 (30)	94 (33)
Diffuse subtype adenocarcinoma	4 (26.7)	2 (16.7)	81 (29)	63 (22)

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Intestinal subtype adenocarcinoma	0	4 (33.3)	44 (16)	70 (25)
Mixed/Unknown subtype	11 (73.3)	6 (50.0)	157 (55)	151 (53)
0 prior therapies	0	0	0	0
1 prior therapy	15 (100)	12 (100)	281 (100)	284 (100)
≥2 prior therapies	0	0	0	0
PD-L1 CPS ≥1	13 (86.7)	11 (91.7)	183 (65)	188 (66)

Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability high; PD-L1, programmed cell death 1 ligand 1.
Source: Chao et al. 2021 (11)

Table 21 ZEBRA study (small intestine cancer) - efficacy outcomes in MSI-H and non-MSI-H subgroups treated with pembrolizumab

	Pembrolizumab	
	Non-MSI-H subgroup, n=32	**MSI-H subgroup, n=4**
ORR, %	8% (2-20) (all patients)	50%
Median DOR (range), months	17.5 (3.0 – 32.1)	28.5 (26.5 – 30.5)
Number of PFS events/Total	31/32	2/4
Median PFS (95% CI), months	2.8 (2.7 – 4.2)	NE (2.5, NE)
Number of OS events/Total	28/32	2/4

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Median OS (95% CI), months	6.6 (4.8 – 12.0)	NE (2.5, NE)

Notes: Within the allcomers study population, three confirmed PRs were observed, of which 2/4 in MSI-H subgroup and one/32 (3%) in patients with MSS/MSI-L status confirmed
Source: Pedersen et al. 2021 (12)

Table 22 KEYNOTE-158 (biliary cancer) - efficacy outcomes in MSI-H and non-MSI-H cohorts treated with pembrolizumab

	Pembrolizumab	
	MSI-H population (cohort K)[a], n=22	**Non-MSI-H population[b], n=104**
ORR, % (95% CI)	40.9 (20.7, 63.6)	5.8 (2.1- 12.1)
DOR, median (range), months	30.6 (6.2 - 46.0+)	NR (6.2-26.6+)
Median PFS (95% CI), months	4.2 (2.1, 24.9)	2.0 (1.9-2.1);
PFS rate, %, 12 months	36.4	5.2
Median OS (95% CI), months	19.4 (6.5, 44.8)	7.4 (5.5-9.6);
OS rate, %, 12 months	63.6	32.7

[a] Data cut-off: 15-OCT-2021; median (range) follow-up: 19.4 (1.1, 60.8) months
[b] Data cut-off: 6-DEC-2018; median (range) follow-up: 7.5 (0.6-34.3) months
Notes: non-MSI-H population includes 99 (95.2) patients with negative MSI status and 5 (4.8) patients with missing MSI status (insufficient tissue for MSI testing, poor quality DNA, testing failure and lack of appropriate consent for necessary genetic testing)
Source: Piha-Paul et al. 2020 (13).

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Table 23 Baseline characteristics for MSI-H and non-MSI-H biliary cancer cohorts treated with pembrolizumab (KEYNOTE-158)

	MSI-H population (cohort K), n=22		Non-MSI-H population, n=104	
	n	%	n	%
Participants in population	22		104	
Sex				
Male	16	73%	51	49%
Female	6	27%	53	51%
Age (Years)				
>= 65	9	41%	44	42.3%
Median	60.5		63	
Range	40 to 77		34 to 81	
Race				
Asian	2	9%	37	35.6%
Black Or African American			0	
White	20	91%	67	64.4%
Missing			0	
ECOG				
[0] Normal Activity	10	46%	42	40.4%
[1] Symptoms, but ambulatory	12	55%	62	59.6%
Number of Prior Lines of Therapy				
0	2	9%	1	1.07%
1	11	50%	42	40.4%
2	6	27%	37	35.6%
3	1	5%	14	13.5%
4	2	9%	8	7.7%
5 or more			2	1.9%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability high

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Notes: non-MSI-H population includes 99 (95.2) patients with negative MSI status and 5 (4.8) patients with missing MSI status (insufficient tissue for MSI testing, poor quality DNA, testing failure and lack of appropriate consent for necessary genetic testing)
Source: Piha-Paul et al. 2020 (13).

Table 24 KEYNOTE-775 (endometrial cancer) - efficacy outcomes in dMMR and pMMR subgroups treated with TPC

	TPC (paclitaxel or doxorubicin)		
	dMMR subgroup, n=65	**pMMR subgroup, n=351**	**All patients, n=416**
ORR, % (95% CI)	12 (5 – 23)	15.1 (11.5 -19.3)	14.7 (11.4 –18.4)
DOR, median (range), mo	4.1 (1.9 – 15.6)	5.7 (0.0 – 24.2)	5.7 (0.0 – 24.2)
Median PFS (95% CI), mo	3.7 (3.1 – 4.4)	3.8 (3.6 – 5.0)	3.8 (3.6 – 4.2)
PFS rate, % (95% CI), 6 months	24.8 (14.3 – 36.8)	36.2 (30.5 – 41.9)	34.3 (29.2 – 39.4)
PFS rate, % (95% CI), 12 months	12.9	13.1 (8.9 – 18.3)	13.2 (9.3 – 17.8)
Median OS (95% CI), mo	8.6 (5.5 – 12.9)	12.0 (10.8 – 13.3)	11.4 (10.5 – 12.9)
OS rate, % (95% CI), 12 months	39.1 (26.7 – 51.3)	49.5 (43.8 – 55.0)	47.9 (42.7 – 53.0)
OS rate, % (95% CI), 24 months	Not available	21.5 (13.9- 30.1)	21.4 (14.2 – 29.6)

Abbreviations: dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; TPC, treatment physician's choice
Source: Makker et al. 2022 (14); EPAR EMEA/H/C/003820/II/0105 (17)

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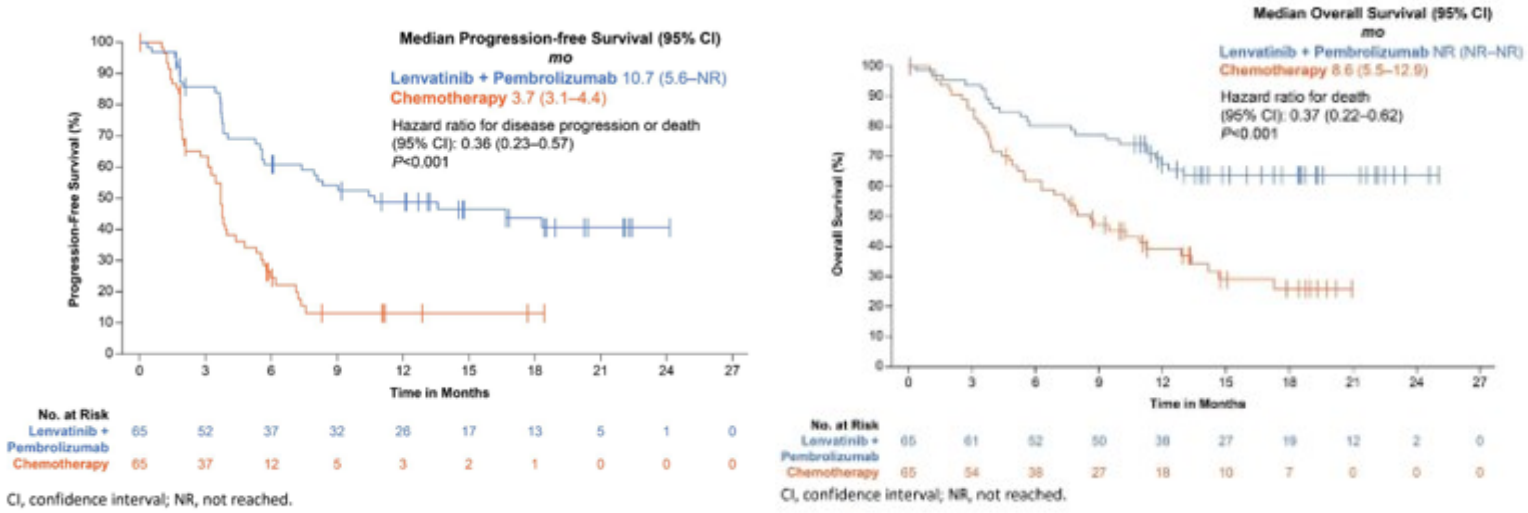
Figure 3 KEYNOTE-775 (endometrial cancer) – KM estimates of PFS (left) and OS (right) in dMMR patients treated with TPC (red curve)



Source: Makker et al. 2022 (14)

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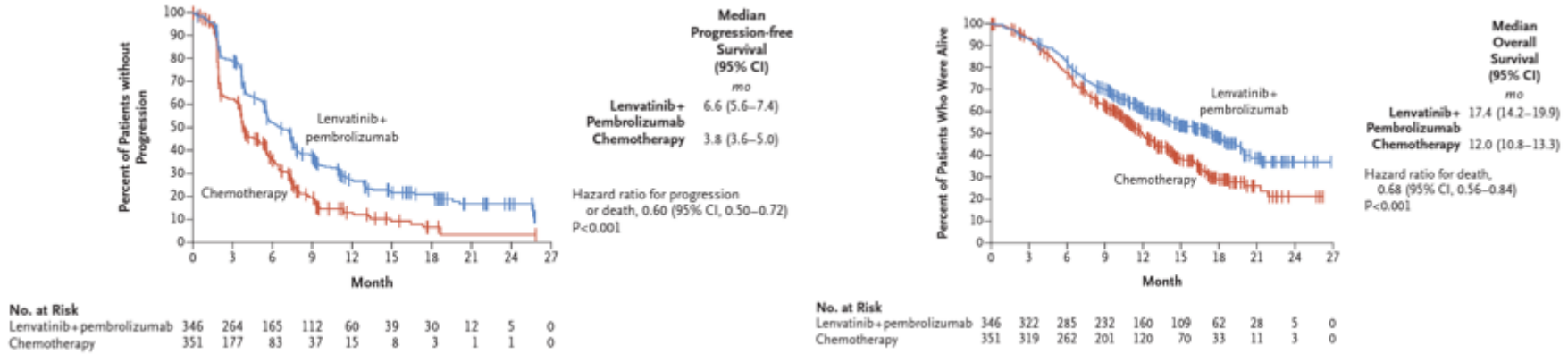
Figure 4 KEYNOTE-775 (endometrial cancer) – KM estimates of PFS (left) and OS (right) in pMMR patients treated with TPC (red curve)



Source: Makker et al. 2022 (14)

Table 25 Baseline characteristics of patients with endometrial cancer treated with TPC (KEYNOTE-775)

	TPC (paclitaxel or doxorubicin)	
	dMMR subgroup, n=65	**pMMR subgroup, n=351**
Median age (range), years	63.0	66 (35-86)
Race*, n (%)		
White	35 (53.8)	211 (60.1)
Asian	12 (18.5)	80 (22.8)
Black	5(7.7)	9 (2.6)
ECOG status, n (%)		
0	34 (52.3)	207 (59.0)

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1	31 (47.7)	144 (41.0)

Abbreviations: dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; pMMR, mismatch repair proficient; TPC, treatment physician's choice
Notes: Data on race were missing for 10.3% patients in the chemotherapy group (pMMR subgroup). Other races or ethnic groups (reported by 4.3% in the pMMR chemotherapy group) included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiple.
Source: Makker et al. 2022 (14)

Table 26 Efficacy outcomes in dMMR subgroup (KEYNOTE-775) vs unselected population (McMeekin 2015) treated with TPC (endometrial cancer)

	TPC (paclitaxel or doxorubicin)		
	dMMR subgroup (KN-775), n=65	**Unselected population (McMeekin 2015), n=248**	**Overall population (KN-775), n=416**
ORR, %(95% CI)	12 (5 – 23)	15.7 (11.2, 21.1)	14.7 (11.4 – 18.4)
DOR, median (range), mo	4.1 (1.9 – 15.6)	Not available	5.7 (0.0 – 24.2)
Median PFS (95% CI), mo	3.7 (3.1 – 4.4)	4.0 (2.7, 4.3);	3.8 (3.6 – 4.2)
Median OS (95% CI), mo	8.6 (5.5 – 12.9)	12.3 (10.7–15.4)	11.4 (10.5 – 12.9)
OS rate, % (95% CI), 12 months	39.1 (26.7 – 51.3)	53	47.9 (42.7 – 53.0)
OS rate, % (95% CI), 24 months	Not available	30	21.4 (14.2 – 29.6)

Source: McMeekin et al. 2015 (15) and Makker et al. 2022 (14)

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the 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 about living with a solid tumour with high microsatellite instability or mismatch repair deficiency or caring for a patient with a solid tumour with high microsatellite instability or mismatch repair deficiency. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.1).

A patient perspective could help either:

Patient expert statement

- 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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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. Please type information directly into the form.

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. 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.

Patient expert statement

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **23 May 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Patient expert statement

Part 1: Living with this condition or caring for a patient with solid tumours with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR)

Table 1 About you, solid tumours with high microsatellite instability or mismatch repair deficiency, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with a solid tumour with high microsatellite instability or mismatch repair deficiency? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with a solid tumour with high microsatellite instability or mismatch repair deficiency? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): I am a Cholangiocarcinoma patient that had a successful Liver Resection in November 2015, followed by 6 months of Chemotherapy.
3. Name of your nominating organisation	AMMF – The Cholangiocarcinoma Charity
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission

Patient expert statement

	☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with a solid tumour with high microsatellite instability or mismatch repair deficiency? **If you are a carer (for someone with a solid tumour with high microsatellite instability or mismatch repair deficiency) please share your experience of caring for them**	I have no direct experience of living with a solid tumour with high microsatellite instability or mismatch repair deficiency but do have direct experience of cholangiocarcinoma. I was diagnosed with Intrahepatic Cholangiocarcinoma (CCA) in October 2015 and at that time there was very limited information available. It was a very traumatic experience to even get to the stage of diagnosis with the lack of expertise in this field at a local hospital. The symptoms I had been displaying were misread as indigestion or muscle strain, even my blood tests were all normal. I was only 44 when diagnosed with CCA, I had been living a healthy lifestyle and always been physically active, so when I was initially given the devastating news that I had just weeks to live it was a huge shock to us all. Thankfully, I managed to push for a 2nd opinion from the team of Liver Specialists at The Queen Elizabeth Hospital in Birmingham and successfully managed to undergo a resection in November 2015 to remove the large tumour from my liver. With no clear treatment pathways available following my surgery, we were left with no other

	viable option than to seek a private consultation with a CCA specialist. Through this private referral I was then able to go on to have a 6-month course of Capecitabine chemotherapy. I was hospitalised 3 times over the 6 months due to some of the adverse side effects from this treatment. If at this stage, I had been able to have had the Molecular Profiling to determine the molecular mutations of my tumour, my treatment could have been quite different. Living with a very rare cancer with limited treatment options has had a dramatic and traumatising impact on my family, especially as there is a high probability of my cancer returning. New targeted therapy treatments are critical to CCA patients like me going forward.
7a. What do you think of the current treatments and care available for solid tumours with high microsatellite instability or mismatch repair deficiency on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. Currently CCA patients here in the UK are left with limited options if they are unable to have a resection. With the lack of current treatment pathways, patients find it exceedingly difficult to get referred to a CCA specialist soon enough for any effect treatment. Within the NHS many CCA patients like me are forced to seek private alternatives. If surgery is not an option, patients are instead offered a chemotherapy combination, which has not changed in a number of years and has had extremely limited success. This treatment which may or may not extend life, often leaves patients with a diminished quality of life, and has a huge impact on both the patient and their families/carers.

	Without Molecular profiling and more targeted treatment therapies like those available in other countries, CCA patients here in the UK will always face an uncertain future. 7b. I am not alone with my frustrations on these limited treatment options available to CCA patients here in the UK. I participate regularly on the online forum 'Cholangiocarcinoma Support (UK & Europe)' and these same views and concerns are echoed across this forum too. CCA is still referred to as a cancer affecting the over 65's. However recent evidence has confirmed that CCA is increasing across all age groups and especially those classed in there 'prime of life'. This point is also echoed on the forums too.
8. If there are disadvantages for patients of current NHS treatments for solid tumours with high microsatellite instability or mismatch repair deficiency (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There are a number of unmet needs for cholangiocarcinoma patients: <u>Effective treatments for CCA are desperately needed.</u> The incidence of this disease is increasing year on year, with mortality mirroring incidence[2], and many younger adults being diagnosed. Currently resection is the only potentially curative treatment, but few are eligible for this. Standard of care 1st line chemotherapy for inoperable CCA patients hasn't changed in years and offers modest, if any, benefit. Currently there is one approved targeted therapy. New and more effective treatments for CCA are desperately needed. <u>Centres of Expertise for CCA patients are needed</u> There seems to be no set pathway/guidance for the care of cholangiocarcinoma patients, many are never seen by those with specialist knowledge, and many are not considered for surgery nor for clinical trials.

	Molecular profiling is needed for all CCA patients Molecular profiling should now be available for all those diagnosed with CCA – at diagnosis or during 1st line treatment. With the advent of targeted therapies and immunotherapies such as pembrolizumab which is effective for those with high microsatellite instability or mismatch repair deficiency, this is essential so that all those eligible for such treatments can be considered in a timely manner. Currently it seems molecular profiling under the NHS is available to only very few CCA patients in the UK, with many seeking this privately.
9a. If there are advantages of pembrolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does pembrolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a. Advantages of this treatment to patients could be life changing. Molecular profiling, leading to a targeted therapy of Pembrolizumab could offer a lifeline to these patients in comparison to the huge side effects from the alternative chemotherapy treatments. Their treatment could mean less time in the hospital and allow patients to be with their families at the same time as receiving treatment, reducing the burden on the NHS. It would allow their quality of life to be improved from being able to spend time with their families and possibly even continue with their daily activities. 9b. Molecular Profiling is needed for all CCA patients at the time of diagnosis to enable the use of more targeted therapies like pembrolizumab in a timely manner, resulting in potentially more lives being saved. 9c. Pembrolizumab would give CCA patients the chance of a targeted treatment plan and pave the way for other similar targeted therapies for those diagnosed with CCA.

10. If there are disadvantages of pembrolizumab over current treatments on the NHS please describe these. For example, are there any risks with pembrolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The main issue is the time factor in diagnosing someone with CCA early enough for them to be considered for this treatment. Although pembrolizumab is effective only for those few with high microsatellite instability or mismatch repair deficiency cancer, for them this treatment is something they know should be effective in extending survival, more so than further chemotherapy, which might or might not be effective for them, or best supportive care.
11. Are there any groups of patients who might benefit more from pembrolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Pembrolizumab is effective for those with high microsatellite instability or mismatch repair deficiency cancer. Those CCA patients without microsatellite instability high or mismatch repair deficient cancers will not benefit from this treatment.
12. Are there any potential equality issues that should be taken into account when considering solid tumours with high microsatellite instability or mismatch repair deficiency and pembrolizumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

Patient expert statement

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	In order for any CCA patient to know if this treatment or that of any other potential targeted therapy could be applicable to them, molecular profiling would need to be available for all CCA patients at diagnosis.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also 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 EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

We consider patient perspectives may particularly help to address this issue. **Inappropriate exclusion of comparators from the company decision problem.** Are there are any comparators not included in the decision problem that you	

consider to be relevant to this appraisal?	
We consider patient perspectives may particularly help to address this issue. **External validity of the trial evidence to the UK target population.** Are the patient characteristics of the trials generalisable to the target UK population?	
Adverse event data for KEYNOTE-158 were aggregated, and not presented for each separate tumour site.	
We consider patient perspectives may particularly help to address this issue. **Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population.**	

Patient expert statement

Do you expect solid tumours with and without MSI-H/dMMR status to respond to differently to treatment? Does the MSI-H/dMMR status worsen prognosis for patients?	
High risk of bias in comparative efficacy because of serious limitations of all methods of survival estimation.	
Populations were aggregated across all tumour sites based on their MSI-H/dMMR status. However, MSI-H/dMMR status for most comparators was unknown and heterogeneity between tumour sites seems substantial.	
Treatment baskets were used to inform standard of care per tumour site, which may bias the costs and outcomes of standard of care in the economic model.	

Patient expert statement

The selection of patients in the comparator studies was not based on their MSI-H/dMMR status, which introduced (methodological) uncertainty in the estimation of the relative effectiveness of pembrolizumab.	
The suitability of the Bayesian hierarchical model approach in the context of this submission was questionable.	
The time-to-death utility approach to model the health-related quality of life of tumour sites included in KEYNOTE-158 was questionable.	
We consider patient perspectives may particularly help to address this issue. **Assumptions regarding the modelling of subsequent treatments were questionable.**	

Patient expert statement

Are the modelled subsequent treatments reflective of UK clinical practice?	
Testing costs to identify patients with MSI-H/dMMR were not included in the company's base-case analysis. Is testing in colorectal cancer and endometrial cancer routinely commissioned in the NHS? Do 50% of patients who have gastric, small intestine, or biliary cancer already receive these tests to identify patients with MSI-H/dMMR?	
Severity estimates were based on the company's modelling of QALYs, which was subject to limitations, and therefore uncertain.	
The majority of the company's scenario analyses could not be reproduced and lacked face validity.	

Patient expert statement

Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Incidence of CCA in increasing, with mortality that parallels incidence.
- Currently there is very little effective treatment for CCA patients.
- Many CCA patients are not considered for surgery nor for clinical trials – 'centres of expertise' are needed for confirmation of diagnosis and treatment pathway, and for molecular profiling.
- All CCA patients should receive molecular profiling at diagnosis or during 1st line treatment
- For those few found to have microsatellite instability high or mismatch repair deficient cancers, pembrolizumab offers a realistic treatment, extending survival with good quality of life.

Thank you for your time.

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 NICE's privacy notice.

Patient expert statement

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Patient expert statement and technical engagement response form

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Information on completing this form

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A patient perspective could help either:

Patient expert statement

- resolve any uncertainty that has been identified OR
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Patient expert statement

Part 1: Living with this condition or caring for a patient with solid tumours with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR)

Table 1 About you, solid tumours with high microsatellite instability or mismatch repair deficiency, current treatments and equality

1. Your name	Helen Morement
2. Are you (please tick all that apply)	☐ A patient with a solid tumour with high microsatellite instability or mismatch repair deficiency? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with a solid tumour with high microsatellite instability or mismatch repair deficiency? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

Patient expert statement

	☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with a solid tumour with high microsatellite instability or mismatch repair deficiency? **If you are a carer (for someone with a solid tumour with high microsatellite instability or mismatch repair deficiency) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for solid tumours with high microsatellite instability or mismatch repair deficiency on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for solid tumours with high microsatellite instability or mismatch repair deficiency	

(for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of pembrolizumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does pembrolizumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of pembrolizumab over current treatments on the NHS please describe these. For example, are there any risks with pembrolizumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from pembrolizumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering solid	

tumours with high microsatellite instability or mismatch repair deficiency and pembrolizumab? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also 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 EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

We consider patient perspectives may particularly help to address this issue. **Inappropriate exclusion of comparators from the company decision problem.** Are there are any comparators not included in the decision problem that you	

consider to be relevant to this appraisal?	
We consider patient perspectives may particularly help to address this issue. **External validity of the trial evidence to the UK target population.** Are the patient characteristics of the trials generalisable to the target UK population?	
Adverse event data for KEYNOTE-158 were aggregated, and not presented for each separate tumour site.	
We consider patient perspectives may particularly help to address this issue. **Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population.**	

Patient expert statement

Do you expect solid tumours with and without MSI-H/dMMR status to respond to differently to treatment? Does the MSI-H/dMMR status worsen prognosis for patients?	
High risk of bias in comparative efficacy because of serious limitations of all methods of survival estimation.	
Populations were aggregated across all tumour sites based on their MSI-H/dMMR status. However, MSI-H/dMMR status for most comparators was unknown and heterogeneity between tumour sites seems substantial.	
Treatment baskets were used to inform standard of care per tumour site, which may bias the costs and outcomes of standard of care in the economic model.	

Patient expert statement

The selection of patients in the comparator studies was not based on their MSI-H/dMMR status, which introduced (methodological) uncertainty in the estimation of the relative effectiveness of pembrolizumab.	
The suitability of the Bayesian hierarchical model approach in the context of this submission was questionable.	
The time-to-death utility approach to model the health-related quality of life of tumour sites included in KEYNOTE-158 was questionable.	
We consider patient perspectives may particularly help to address this issue. **Assumptions regarding the modelling of subsequent treatments were questionable.**	

Patient expert statement

Are the modelled subsequent treatments reflective of UK clinical practice?	
Testing costs to identify patients with MSI-H/dMMR were not included in the company's base-case analysis. Is testing in colorectal cancer and endometrial cancer routinely commissioned in the NHS? Do 50% of patients who have gastric, small intestine, or biliary cancer already receive these tests to identify patients with MSI-H/dMMR?	
Severity estimates were based on the company's modelling of QALYs, which was subject to limitations, and therefore uncertain.	
The majority of the company's scenario analyses could not be reproduced and lacked face validity.	

Patient expert statement

Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Please Note: I have responded fully under the Patient Organisation submission (AMMF – The Cholangiocarcinoma Charity) and as all responses given there would concur with those I would give as Patient Expert, please refer to that submission.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, 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 EAR and stakeholder responses are used by the committee to help it make decisions at the 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 for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

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.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. 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.

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. 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.

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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **23 May 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

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.

Part 1: Treating solid tumours with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Kai-Keen Shiu
2. Name of organisation	UCLH NHS Foundation Trust, UK
3. Job title or position	Consultant Medical Oncologist, Gastrointestinal Oncology Servic
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 solid tumours with high microsatellite instability or mismatch repair deficiency? ☒ A specialist in the clinical evidence base for solid tumours 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 encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not 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.	None

Clinical expert statement

8. What is the main aim of treatment for solid tumours with high microsatellite instability or mismatch repair deficiency? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	In advanced/inoperable or metastatic disease control and shrink the cancer, delay progression and in some patients achieve durable response, cancer remission
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)	Either 1) tumour response ie shrinkage of more than 20-30%, 2) tumour stability and improvement on disease related symptoms 3) Both 1 or 2 for more than 3 months.
10. In your view, is there an unmet need for patients and healthcare professionals in solid tumours with high microsatellite instability or mismatch repair deficiency?	Yes. My view is that all patients should be tested for MMR as it's a cheap,readily available test, MSI testing if available and access to immunotherapy treatment as early as possible in their treatment pathway as the clinical benefits are superior to SOC systemic therapies including quality of life/toxicity profil
11. How are solid tumours with high microsatellite instability or mismatch repair deficiency currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	1st line Pembrolizumab for dMMR mCRC 2nd line Nivolumab-Ipiliumumab for dMMR mCRC (if they had 1st line chemotherapy and no 1st line immunotherapy I cannot speak on the non-GI indications, but for non-CRC GI dMMR patients the only access prior to this evaluation was due COVID pandemic when we had access to Nivolumab in any line for dMMR CRC, Oesophagogastric and Hepatobiliary and small bowel cancers.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No – as the access program to Nivolumab is now closed. • Treatment is given iv 3 or 6 weekly over 30-60 minutes which is less time in hospital than SOC systemic therapies, the side effect profile is see toxic so less likely to have hospital admissions and benefits are greater

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	so delays time to death, and quality of life, ability to work etc better than SOC treatments. • Secondary care prescribed and managed by oncologists • Nothing new as immunotherapy including Pembrolizumab is already used for NHS patients in other tumour types which are not dMMR, e.g lung, melanoma, oesophoageal-gastric squamous cell and adenocarcinomas
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• Yes – significantly • Yes - significantly
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not that I am aware of. Just need biomarker of dMMR and/or MSI-High
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 clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier – see answer 12 too.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treat to progression or unacceptable side effects up to 2 years. No additional testing other than to ensure patients are not stopped prematurely due to pseudoprogression so confirmatory scan 4-6-8 weeks later to confirm progression if patient is clinically doing well/other markers of response are good.
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? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	No. Should allow 6 weekly Pembrolizumab as well as 3 weekly Pembrolizumab which saves time and costs for patients and healthcare.
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 is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	• Yes • Yes – there is currently no access for these patients to have immunotherapy in 3rd line/chemorefractory setting for dMMR mCRC, or in any line for the other tumour types being appraised.
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?	Drug is already commonly used for other tumour types in the NHS so I don't envisage any problems for management of side effects for patients and in general the quality of life will be superior on immunotherapy than alternate SOC systemic treatments due to lower toxicity profile, shorter same day treatments, longer intervals between treatments and if a response, a durable response/possible achieve remission which is extremely unlikely to be achieved with SOC systemic chemotherapy treatments.
20. Do the clinical trials on the technology reflect current UK clinical practice?	No. Although the trials have been mainly smaller, phase 2 and non randomised, the magnitude of benefit again historical controls/trials has meant that FDA has

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	approved any patient who has a dMMR/MSI-High cancer who has had at least 1 line of standard treatment for advanced disease to have immunotherapy. It is unlikely that randomised Phase 3 trials will be performed as it's felt to be unethical in these small subgroups of patients where the rationale and known benefits of immunotherapy are already seen to be superior in the phase 2 trials. • Response rate, progression free survival, duration of response • A surrogate marker is usually that if a patient achieves a partial or complete response within 3-4 months they will achieve a durable response • 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 of NICE technology appraisal guidance [TA405 and TA866]?	No
23. How do data on real-world experience compare with the trial data?	Very little published RWE of large cohorts as rare subgroup.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Only to ensure all patients who have these tumour types have MMR or MSI testing as early as possible in their diagnostic pathway – ideally at first diagnosis of their cancer. • No • No • No

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, 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 committee meeting.

For information: the professional organisation that nominated you has also 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 EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Inappropriate exclusion of comparators from the company decision problem. Should nivolumab and ipilimumab, irinotecan and raltitrexed be included in decision problem as relevant comparators for colorectal cancer? Please identify any established clinical management options	1) Nivolumab and Ipilimumab in the Checkmate 142 trial in 2nd line was not randomised against 2nd line chemotherapy, only Nivolumab monotherapy. The response rate and PFS was superior to Nivolumab and although cross trial comparisons to the KEYNOTE 164 trial of 2nd line Pembrolizumab should be taken with caution, the ORR and PFS of Pembrolizumab in KEYNOTE 164 and Nivolumab in Checkmate 142 are broadly/essentially the same (from a therapeutic 'class' they are both PD1 inhibitors and no evidence that one is better yet than the other – pending 1st line 8HW trial results in patients with dMMR/MSI-high mCRC. 2) It is relevant to be aware of the superiority of Nivo-Ipi over Pembro in second line, there will be clinical scenarios were the clinician and/or patient would not want to have second line doublet immunotherapy due to increase risk of toxicities including colitis, hepatitis, pneumonitis and endocrinopathies. This could be due to pre existing non cancer related co-morbidities, or direct disease related frailty including obstructing tumour/high output stoma (higher risk of severe diarrhoea/colitis) or diffuse liver disease causing significant liver dysfunction (higher risk of hepatitis).

Clinical expert statement

for each of the tumour sub-populations that have not been included amongst the specified comparators in the decision problem.	3) Therefore it would be valuable option for patients to access PD1 monotherapy in 2nd or in 3rd line/chemorefractory setting as RR, PFS and OS superior to ANY 2nd line chemotherapy option – whether this includes irinotecan (usually with 5FU/Capecitabine), raltirexed (usually used with Oxaliplatin or Irinotecan in the metastastic setting) , or last line vs Regorafenib or Trifluridine and Tipiracil . There is more data as well as mature survival data from KEYNOTE 164 to support Pembrolizumab in 2nd and 3rd line than Nivolumab. 4) Overall, it's important that no patient who has dMMR/MSI-High advanced bowel should miss out on the opportunity to access immunotherapy in 1st, 2nd line or in chemorefractory setting at least once.
External validity of the trial evidence to the UK target population. Are the patient characteristics in the clinical trials representative of the UK target population? Is ethnicity a potential effect modifier in these target populations?	Are the patient characteristics in the clinical trials representative of the UK target population? Yes Is ethnicity a potential effect modifier in these target populations? No, not that I am aware of/or of the extant data re any specific patients' ethnicity responding better/worse and/or be a confounder
Adverse event data for KEYNOTE-158 were aggregated, and not presented for each separate tumour site.	That is true, but no clear evidence that in GI cancers which are dMMR/MSI-High the immunotherapy related side effects would be significantly different – the main ones remain risk of colitis, hepatitis and endocrinopathies as per KEYNOTE 177 trial

Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population. Is MSI-H/dMMR status a treatment effect modifier? Does the MSI-H/dMMR status worsen prognosis for patients?	No evidence that if a patient truly has a dMMR or MSI-H tumour that there is any difference in response. However, MSI-High testing more likely to allow more patients to access immunotherapy as it is a DNA based 'binary' read result, whereas IHC interpretation can be confounded by quality of archived tissue, expertise of the histopathologist interpreting the results. Possibly 2-3% of patients are labelled as dMMR when they are MSS, as well as 2-3% of patients labelled as pMMR when they are MSI-High. Inherently, it is hard to ascertain whether MSI-H/dMMR predicts worse prognosis in advanced setting than MSS/pMMR as this has not been 'tested' as 1) it remains a small subgroup of any observational or therapeutic advanced cancer trial. 2) We do not give immunotherapy to pMMR/MSS patients as it has shown no/very limited efficacy. 3) However standard of care chemotherapy based options in these non-CRC patients have worse outcomes than patients who can/would receive immunotherapy on KEYNOTE 158 trial
High risk of bias in comparative efficacy.	
Populations were aggregated across all tumour sites based on their MSI-H/dMMR status. However, MSI-H/dMMR status for most comparators was unknown and heterogeneity between tumour sites seems substantial.	Tumour heterogeneity remains an issue and uncertainty principle is acknowledged however the clincal and biological rationale/mechanism of action of checkpoint inhibitors of dMMR/MSI-High cancers (regardless of specific tumour type) of why they would be better than any standard of care systemic therapy or best supportive is strong. I would recommend you look at the following trials (if not already) to see the benefit of Pembrolizumab in dMMR/MSI-High Gastric cancers (KEYNOTE 59, 61 and 62) in summary; ' At data cutoff, median follow-up durations were 5.6 months (range = 0.5----–37.6 months) in KEYNOTE-059, 7.9 months (range = 0.2–27.7 months) in KEYNOTE-061, and 11.3 months (range = 0.2–41.2 months) in KEYNOTE-062.

Clinical expert statement

	In KEYNOTE-059 (third-line treatment or higher), 7 (4.0%) of 174 patients had MSI-H tumors. Among these patients, median overall survival was not reached (95% confidence interval [CI] = 1.1 months–not reached), median progression-free survival was not reached (95% CI = 1.1 months–not reached), and objective response rate was 57.1%. In KEYNOTE-061 (second-line treatment), 27 (5.3%) of 514 patients had MSI-H tumors, including 15 patients in the pembrolizumab group and 12 in the chemotherapy group. Median overall survival was not reached with pembrolizumab (95% CI = 5.6 months–not reached) vs 8.1 months (95% CI = 2.0–16.7 months) with chemotherapy alone. Median progression-free survival was 17.8 months (95% CI = 2.7 months–not reached) vs 3.5 months (95% CI = 2.0–9.8 months). Objective response rates were 46.7% vs 16.7%. In KEYNOTE-062 (first-line treatment), 50 (7.3%) of 682 patients had MSI-H tumors, including 14 in the pembrolizumab group, 17 in the pembrolizumab/chemotherapy group, and 19 in the chemotherapy group. Median overall survival was not reached with pembrolizumab monotherapy (95% CI = 10.7 months–not reached) or with pembrolizumab/chemotherapy (95% CI = 3.6 months–not reached) compared with 8.5 months (95% CI = 5.3–20.8 months) with chemotherapy alone. Median progression-free survival was 11.2 months (95% CI = 1.5 months–not reached) for pembrolizumab and not reached (95% CI = 3.6 months–not reached) for pembrolizumab/chemotherapy, compared with 6.6 months (95% CI = 4.4–8.3 months) for chemotherapy alone. Objective response rates were 57.1% for pembrolizumab, 64.7% for pembrolizumab/chemotherapy, and 36.8% for chemotherapy alone. For dMMR/MSI-High Small bowel cancers – ZEBRA trial Clin Cancer Res 2021 Jul 1;27(13):3641-3648. doi: 10.1158/1078-0432.CCR-21-0159. Epub 2021 Apr 21.Abstract

	Purpose: Small-bowel adenocarcinoma (SBA) is rare, and no standard of care exists for metastatic disease beyond first-line FOLFOX/CAPOX. SBA has higher rates of microsatellite instability (MSI-H) and T-lymphocyte infiltration than other gastrointestinal cancers. We hypothesize that pembrolizumab, a PD-1 inhibitor, will induce antitumor response. Patients and methods: Patients with previously treated advanced SBA received pembrolizumab 200 mg i.v. every 3 weeks until disease progression (PD), toxicity, or 35 doses maximum. Primary endpoint was confirmed overall response rate (ORR) with secondary progression-free survival (PFS), overall survival (OS), and toxicity assessment endpoints. Outcomes were stratified by tumor location, microsatellite stability (MSS) or instability (MSI-H), and PD-L1 level. Results: Forty patients were treated for a median duration of four cycles (range, 1-35). All patients are off study treatment due to PD (75%), death (10%), 35 cycles completed (8%), refusal (3%), and adverse effects (AEs, 5%). Three confirmed partial responses [PRs; 8%; 95% confidence interval (CI), 2-20] did not meet predefined success criteria of ORR 30%. Median OS (7.1 months; 95% CI, 5.1-17.1) and median PFS (2.8 months; 95% CI, 2.7-4.2) were similar across primary tumor sites. One confirmed PR (3%) was seen in patients with low MSS/MSI tumors and correlated with high tumor mutation burden (TMB). Fifty percent of patients with MSI-H tumors achieved PR and remain alive without progression. Twenty-five patients (63%) had grade ≥3 AEs and 11 patients (28%) had grade 4/5 AEs. Conclusions: In the largest study of SBA to date, pembrolizumab did not induce the hypothesized response rate; however, we did identify responses in key biomarker-selected cohorts. I know of no data around immunotherapy for bile duct cancers but the 1st line TOPAZ trial of Cis-Gem-Durvalumab and KEYNOTE 966 trial of Cis-Gem-Pembrolizumab has shown clinical benefit in an unselected group of patients. I suspect there wil be sub group analysis of patient who are dMMR/MSI-

	High in both those trials to show they benefited more from the combination and maintenance immunotherapy.
Treatment baskets were used to inform standard of care per tumour site, which may bias the costs and outcomes of standard of care in the economic model.	Agree, but there remains at least 10-20% chance of response and promise of a prolonged durable response with less toxicties with Pembrolizumab in 2nd line and beyond, vs any of the standard of care options which are worse. E.g. 10-15% response to 2nd line taxol in gastric cancer, and <10% chance of response to 2nd line chemo for SBA (FOLFIRI) and BTC (FOLFOX). There will also be a significant minority of response who may achieve a 'complete' response/go into remission within 2 years, and maintain that remission after stopping immunotherapy which is almost never seen (<5%) in patients who have standard chemotherapy based treatments.
The selection of patients in the comparator studies was not based on their MSI-H/dMMR status, which introduced (methodological) uncertainty in the estimation of the relative effectiveness of pembrolizumab.	True, but as stated above, as the percentage of patients in those comparator studies would be very small approx. 5%), even if we could get that subgroup analysis the numbers would be too small to estimate relative effectiveness. What we do know at least from KEYNOTE 177 in 1st line/phase 3 trial, that Pembrolizumab is more effective than 1st line chemotherapy. See my answer above re comparators in the gastric and SBA trials.
The suitability of the Bayesian hierarchical model approach in the context of this	Not able to really comment as not a statistician.

submission was questionable.	
The time-to-death utility approach to model the health-related quality of life of tumour sites included in KEYNOTE-158 was questionable.	Can't really comment – but happy to do this at consultation and can look at the data from KEYNOTE 59, 61, 62 and ZEBRA before the consultation
Assumptions regarding the modelling of subsequent treatments were questionable. Are the proportions of patients receiving subsequent treatments equal regardless of initial treatment? Are the modelled subsequent treatments reflective of UK clinical practice?	I think it's very hard to really model subsequent lines of treatments, as there is some heterogeneity in clinical practice of what chemotherapy type and combinations given. The type of treatment is based on many factors including what the patient had in first line, the clinical benefits including amount of tumour shrinkage/tumour volume/sites of metastatic disease, time to progression on or off treatment, toxicity of that initial treatment, hang over toxicity from that treatment and finally performance status/fitness of patient to have more lines of chemotherapy. In general I would say that as immunotherapy has less side effects that would impact/worse performance status than more chemotherapy it's a favourable option if available.
Testing costs to identify patients with MSI-H/dMMR were not included in the	CRC is routinely commissioned. I think endometrial is but you would have to ask the Gynae-clinical expert

company's base-case analysis. Is testing in colorectal cancer and endometrial cancer routinely commissioned in the NHS? Do 50% of patients who have gastric, small intestine, or biliary cancer already receive these tests to identify patients with MSI-H/dMMR?	• MSI-H and dMMR is not commissioned nor done routinely for the non-CRC GI tumour subtypes but really ought too. If this appraisal is positive then pathologist will have to test routinely/reflex otherwise would be denying a potential treatment option to these patients.
Severity estimates were based on the company's modelling of QALYs, which was subject to limitations, and therefore uncertain.	Agree – hard to quantify that accurately as answered above
The majority of the company's scenario analyses could not be reproduced and lacked face validity.	Agree – uncertainties have to be addressed and acknowledged though unsure panel will find much better evidence in extant data available/published.
Are there any important issues that have been missed in EAR?	No

Clinical expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is an unmet need for these patient with dMMR/MSI-High cancers to access and benefit from immunotherapy
It is innovative and life changing allowing some patient to have the possibility of long and productive lives
We should lead the way (outside of the USA/FDA) in properly appraising the evidence and making an informed decision on access to immunotherapy based on this agnostic biomarker
It will encourage/enforce MMR testing to be done routinely/quickly which not only gives access to therapy but will increase diagnose of Lynch Syndrome which has societal benefits in cancer surveillance/prevention
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR 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 evaluation, 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.

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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.

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. 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.

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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **23 May 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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.

Technical engagement response form

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About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Merck Sharp & Dohme (MSD) UK Limited**
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

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Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG response
Issue 1: Inappropriate exclusion of comparators from the company decision problem.	No	**It is important to note that pembrolizumab is consistently cost-effective compared with all SOC chemotherapy comparators in all tumour sites, including under exploratory worst-case scenarios (see response to issue 5 and results in Table 2).** **However, the available evidence and clinical opinion suggest that nivolumab and ipilimumab would be the preferred option in clinical practice for patients with metastatic CRC who have been previously treated with chemotherapy, given the superior efficacy of this combination compared to immunotherapy alone. Therefore, MSD accept a restricted recommendation in CRC for this small (and shrinking) group who have not had pembrolizumab previously.** **Irinotecan and raltitrexed, either alone or in combination, are not considered relevant comparators as these are rarely used in clinical practice. This is well-established**	The company now agree with the EAG that nivolumab with ipilimumab is an appropriate comparator to pembrolizumab for CRC. They have also stated that pembrolizumab would not be an appropriate treatment for any CRC patients in the population for this appraisal given the superiority of nivolumab with ipilimumab, except where patients are unsuitable for treatment with nivolumab with ipilimumab. The questions would then be whether patients might ever be judged in clinical practice to be unsuitable for nivolumab with ipilimumab, what the appropriate comparators are for this subgroup and the relative effectiveness and cost effectiveness of pembrolizumab vs. these comparators. The EAG cannot answer the first question and would note

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		and supported by clinical expert opinion and previous appraisals. Nivolumab with ipilimumab (CRC) As per Blueteq, metastatic MSI-H/dMMR colorectal cancer (CRC) patients are not eligible for nivolumab with ipilimumab if they have previously received an anti-PD-1 antibody therapy such as pembrolizumab as first-line treatment. Internal market share estimates suggest that almost [redacted] of metastatic MSI-H/dMMR CRC patients receive pembrolizumab in first line. Chemotherapy is only offered as first-line treatment when the outcome of the MSI-H/dMMR testing is still unknown or where the progression of disease requires a fast response. Nivolumab with ipilimumab represent the second-line treatment of choice for the small subset of metastatic MSI-H/dMMR CRC patients previously treated with chemotherapy and that are suitable for this immunotherapy and CTL-4 combination. The pivotal CheckMate 142 study showed nivolumab and ipilimumab to have far superior efficacy to nivolumab alone (OS and PFS KM curves were > 20% points above nivolumab alone for 6.5 years, see figures below). Pembrolizumab OS/PFS results from KEYNOTE-164 are very similar to those seen for nivolumab in CheckMate 142 and so the combination is superior to immunotherapy alone. Exploratory unanchored MAIC results comparing pembrolizumab with the combination also supported this conclusion: PFS HR of [redacted] and OS HR [redacted]. Clinicians also agreed that the nivolumab and ipilimumab combination is preferred to an immunotherapy alone given the better efficacy achieved when adding a CTLA-4 targeting	that no evidence has been presented to directly answer the second and third. The EAG would therefore point out that any evidence that has been presented for the comparison of pembrolizumab with any comparator in CRC was not specifically for this nivolumab with ipilimumab unsuitable subgroup. If this evidence is judged to be applicable to this subgroup, then all EAG critique relating to it would also be applicable, including the appropriateness of not including irinotecan or raltitrexed as comparators. In response to this specific point, the company continue to argue that these two treatments alone or in combination are not appropriate comparators and have reiterated that this is due to little use in clinical practice. They have also added some evidence of the effectiveness of these two treatments, the conclusion of the company being that: *"…similar efficacy (or lower) is consistently observed and therefore the cost-effectiveness analysis would most likely give comparable or more favourable ICERs."* However, the EAG note the following problems with the evidence: • It is not part of a systematic review and therefore subject to a form of selection bias in terms of both studies and outcomes included.

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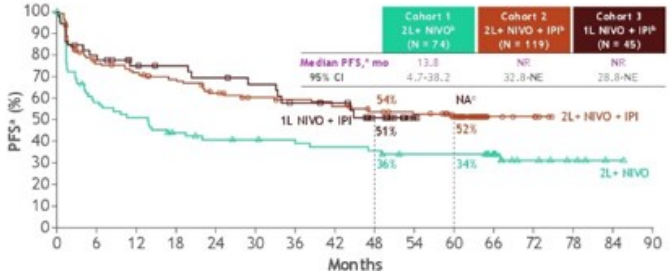
		treatment. Therefore, there is very little (if any) unmet need in this very small patient population that would be met by pembrolizumab. It is possible that some of these patients may have a degree of autoimmune-related comorbidities which make them unsuitable for a dual immunotherapy and CTLA-4 combination. While for these patients nivolumab with ipilimumab is not appropriate (i.e., it is not a relevant comparator), pembrolizumab would be an alternative treatment option, subject to this appraisal. **MSD would accept a recommendation for pembrolizumab in CRC that is restricted to those patients who are unsuitable for treatment with nivolumab and ipilimumab.** <u>CheckMate 142 OS/PFS results comparing nivolumab and ipilimumab (orange) and nivolumab alone (green)</u> Figure 2. Progression-free survival  	• It has not been included in a cost effectiveness analysis and so the effect of any trade-off between effectiveness outcomes or between effectiveness and cost has not been assessed such that the effect on the ICER is unknown. The ambiguity as to whether ECM is a separate comparator to the specific ones listed by the company has been resolved, notwithstanding the unresolved key issue regarding which specific comparators should have been included.

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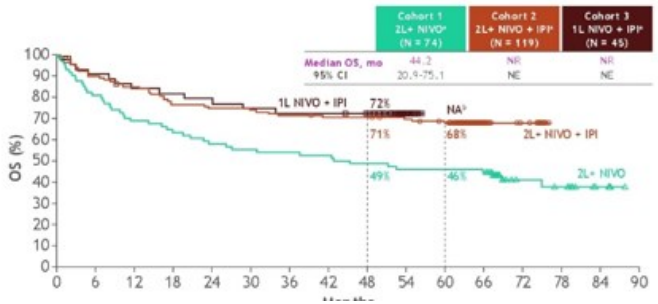
		Figure 3. Overall survival  <u>Irinotecan and raltitrexed (CRC)</u> Irinotecan and raltitrexed, either alone or in combination, are not considered relevant comparators as these are rarely used in clinical practice where 5-fluorouracil and folinic acid-based regimens (one of the relevant comparators in this appraisal for colorectal cancer) are either not tolerated or inappropriate. This is well-established with the consensus also reached in previous appraisals of technologies in previously treated CRC patients where clinical experts clarified that single-agent irinotecan is rarely used because of the toxicities compared with other options whereas raltitrexed is rarely used in clinical practice for specific populations only, such as for people with a history of heart disease or who develop angina on 5-FU-based chemotherapy (1). Also, when used with other treatments, the dose of irinotecan can be lower and therefore better tolerated than when used as monotherapy (2). Moreover, neither raltitrexed nor irinotecan are indicated as suitable treatments in metastatic colorectal cancer in current NICE guideline (NG151) (3).	

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		Raltitrexed and irinotecan have shown similar or lower efficacy compared to other available options, with irinotecan also showing worse toxicity: Raltitrexed • In a randomised controlled trial (RCT) evaluating raltitrexed vs 5-FU+ leucovorin in patients with advanced recurrent metastatic adenocarcinoma of the colon or rectum, there was **no significant difference** between the two groups in overall survival (HR=1.056 [95% CI: 0.847, 1.317]) and time to progression (HR=1.08 [95% CI: 0.889, 1.311]) (4); • In a comparative study of raltitrexed versus a standard 5-FU plus high-dose leucovorin regimen (the Machover regimen) in patients who had advanced recurrent or metastatic adenocarcinoma of the colon or rectum and had not received prior systemic cytotoxic therapy for advanced disease, while the objective tumour response rate was similar in both treatment groups (18.6% of raltitrexed patients vs 18.1% of 5-FU + leucovorin patients), the **median OS favoured the 5-FU + leucovorin** (10.9 months for raltitrexed patients vs 12.3 months for 5-FU + leucovorin patients ; HR=1.15 [95% CI: 0.93, 1.42]); the **median PFS also favoured 5-FU + leucovorin** (3.9 months for raltitrexed patients vs 5.1 months for 5-FU + leucovorin patients; HR=1.33 [95% CI: 1.09 to 1.62]) (5); Irinotecan • In a phase II trial in patients with advanced colorectal cancer previously treated with a fluoropyrimidine and randomly allocated to either single-agent irinotecan or	

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		FOLFIRI, there was **no statistically significant difference** between the treatment arms in progression-free survival (HR = 0.81 [95% CI: 0.52, 1.25]; p = 0.34) or overall survival (HR= 0.72 [95% CI: 0.46, 1.12]; p = 0.14) (6); • In a single-arm study in patients with advanced colorectal cancer, single agent irinotecan showed **only modest activity** in patients with prior 5-FU exposure. Of the total 90 patients entered in the previously treated group, 12 (13.3% [95%CI: 7.1, 22.1) experienced a partial response to irinotecan therapy, with a median OS of 8.3 months (range: 0.36 to 34.8). Gastrointestinal and hematologic side effects were reported as the leading toxicities seen with irinotecan (7); • In a non-randomized, open-label phase II clinical trial in patients with mCRC after failure with oxaliplatin and fluoropyrimidine or its derivatives treated with irinotecan and raltitrexed intravenously, the overall response rate was 8.6%, and the disease control rate was 71.4%. The **median PFS was 4.5 month**s (95% CI: 3.8, 5.2) while the **median OS was 12.0 months** (95% CI: 8.5, 15.5) (8). When comparing these results with those for the comparators relevant to this appraisal (pooled FOLFIRI/FOLFOX/FOLFOX4/m-FOLFOX-6 and TAS-102), based on the ITC presented in the submission, similar efficacy (or lower) is consistently observed and therefore the cost-effectiveness analysis would most likely give comparable or more favourable ICERs. <u>Established clinical management (ECM) without pembrolizumab</u>	

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		MSD agree with EAG definition of ECM as "a general term for any comparator, provided it is currently used in clinical practice in England and Wales". In the decision problem table (Table 1 of document B in company submission) as well as in the clarification question responses (response to question B4a), the comparators that are considered to represent the standard of care in the UK in the licensed indications (i.e., the ECM) were listed. These are based on main clinical guidelines and were further validated by clinical experts. As such, the wording "ECM" was replaced with specific comparators that pembrolizumab would replace in clinical practice, subject to this appraisal. This was carried out for each tumour site including small intestine, biliary and gastric cancers. For the treatments indicated by NICE as relevant to the appraisal but that are not considered relevant comparators, a clear justification for their exclusion has been provided above (for nivolumab with ipilimumab, raltitrexed and irinotecan in CRC), in the submission (Table 1 of document B in company submission) and in the clarification questions (responses to questions A18 and B4a). Also, clinical experts when consulted did not identify any other treatments that would represent current practice in the UK. Therefore, we believe that the evidence provided is based on an exhaustive list of treatments that are considered relevant comparators and there are no other treatments being part of the ECM that have been missed.	
Issue 2: External validity of the trial evidence to	Yes	**This issue is considered resolved following technical engagement given that no evidence suggesting ethnicity to be a treatment effect modifier is found, and therefore**	The company states that, "no meaningful evidence of differences in ORR between race groups is found in the subgroup

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the UK target population.		**the efficacy outcomes are considered generalisable to the population in the UK.** **The requested subgroup analyses for ethnicity are descriptive and exploratory and, considering that they have been conducted in very small groups of patients, no meaningful conclusions can be drawn about the effectiveness of the technology in these subgroups.** Differences are noted in the proportion of race groups between the trials and the UK cancer incidence data mainly for **colorectal cancer** (67.7% vs 90% White, 26.6% vs 2.1% Asian and 5.6% vs 1.4% Black in KEYNOTE-164 and UK incidence data, respectively) and **gastric cancer** (63% vs 88% White, 28% vs 3.0% Asian and 4% vs 2.7% Black in KEYNOTE-158 and UK incidence data, respectively). In contrast, no substantial differences are observed for the other tumour sites. While the distribution of the baseline characteristics may be affected by the small sample size of the trial population for each tumour site, overall the population in both trials is considered broadly representative of UK patients for the same indications. Moreover, caution should be taken when comparing two different data sources, especially considering that cancer incidence data by ethnicity may fail to capture cancers being diagnosed later in non-White minority ethnic groups so may not reflect the actual incidence. Subgroup analyses by race group are presented in Appendix A below (Table 4Table 9). It should be noted that, due to the very small sample size for some race groups (e.g., 3 and 2 Asian patients in the small intestine and biliary group,	analysis in any of the tumour sites, with the ORR 95% CIs mostly overlapping". The EAG disagree that there was no evidence of a difference in outcomes between the ethnic sub-groups. In gastric cancer, for example, [redacted]% of white patients died, compared to [redacted]% of Asian patients and [redacted]% of 'other' patients. These are, of course, point estimates for small groups, and so the EAG fully accept that there is a certain probability that the apparent differences could merely represent sampling error. However, this is by no means certain, so these observations should not be dismissed. The company has not formally estimated the probability of a type I error by subjecting the differences between sub-groups to formal statistical analysis. The company's approach of evaluating the overlap of 95% CIs is naïve and demonstrates relatively little, as it is quite possible for there to be a significant ($P<0.05$) difference between groups when the 95% CIs of the compared groups are overlapping. Furthermore, the small sample sizes mean that even if no statistically significant difference were seen between sub-groups, the probability of a type II error secondary to insufficient

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		respectively), in some cases it was necessary to group multiple race groups into a single subgroup “non-White” to allow less imprecise estimates. These subgroup analyses are descriptive, exploratory, not pre-specified analyses conducted in very small subgroups, and therefore caution should be taken when drawing conclusions about efficacy outcomes in different race groups based on these findings. In particular, the non-White/Other subgroups in most of the tumour sites are very small (2, 5 and 5 participants in biliary, small intestine and gastric cancer, respectively) with the median PFS and OS estimates based on a low number of events, so these results may be due to chance and are not considered informative. No meaningful evidence of differences in ORR between race groups is found in the subgroup analysis in any of the tumour sites, with the ORR 95% CIs mostly overlapping. As anticipated, the very small sample size for non-White patient subgroups in small intestine and biliary cancers resulted in a wider 95% CI. As the subgroups analyses show no evidence suggesting ethnicity to be a treatment effect modifier, the difference in proportions between the trials and UK population is not expected to affect the external validity of the trial results and efficacy outcomes are considered generalisable to the population in the UK.	statistical power would still make dismissal of any sub-group differences inappropriate. The EAG thinks it is important that the committee appreciate that these point estimate differences *may* be important and that they should therefore be considered in the context of applicability, rather than dismissed from discussion. This is particularly important in this example, as the trial data for gastric cancer included 28% Asian participants, compared to an estimated 3% of Asians in the UK target population. Because the trial sub-group analyses showed better results for this outcome in Asians, it does appear possible that the higher proportion of Asians in the trial data may be over-estimating benefits in the UK target population. Perusal of the sub-group analysis results in Appendix A demonstrates several other important point-estimate differences between sub-groups. Examples are ‘complete response’ and ‘partial response’ in gastric cancer, ‘complete response’ in endometrial cancer, and % of PFS events in gastric cancer. The EAG therefore do not agree that this issue can be considered to be resolved.

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Issue 3: Adverse event data for KEYNOTE-158 were aggregated, and not presented for each separate tumour site.	Yes	**This issue is considered resolved following technical engagement. Based on the safety results reported by tumour site, no meaningful differences can be detected in the frequency and type of adverse events across the tumour sites. The AE and AEOSI reported are also generally consistent with the well-known safety profile of pembrolizumab monotherapy.** The safety data were aggregated to increase the sample size and allow more meaningful estimates of adverse event (AE) incidence. The AEs, including adverse events of special interest (AEOSI), reported in the KEYNOTE-158 trial for each tumour site are presented in Table 10Table 18. It should be noted that, due to the small sample size of the tumour site groups, the frequency of AEs, particularly of those that are less common, may not be indicative of the actual incidence of these adverse events in these indications and may be a spurious effect so no clear trend can be detected; therefore, the results should be interpreted with caution. With regard to the more common AEs, the frequency and type of adverse events did not vary substantially across the tumour sites, with diarrhoea, fatigue, vomiting, abdominal pain, arthralgia and pruritus being consistently reported within same range of frequency ([redacted] in all tumour sites. These adverse events are also reported as very common AEs associated with pembrolizumab monotherapy in the Summary of Product Characteristics (SmPC). The majority of the other AEs reported with an incidence ≥5% in each tumour site are also presented as very common or common in the SmPC. The proportion of participants with Grade ≥ 3 AEs ranged from [redacted] to [redacted] across all tumour sites, with few Grade ≥ 3 AEs being reported with a frequency greater than 5%.	Despite the company's statement that the tumour sites did not vary substantially in terms of AE prevalence, there appear to be substantial differences in AE profile between tumour sites. For brevity, the discussion will focus on the common AEs highlighted by the company. For example, the biliary cancer group had a much higher rate of vomiting ([redacted]%) than those with gastric cancer ([redacted]%). There were also differences between sites in diarrhoea ([redacted]% in small intestine but [redacted]% in gastric), fatigue ([redacted]% in endometrial but [redacted]% in gastric), abdominal pain ([redacted]% in biliary but [redacted]% in endometrial), arthralgia ([redacted]% in endometrial but [redacted]% in small intestine) and pruritis ([redacted]% in endometrial but [redacted]% in gastric). These differences are important because they highlight the high site-specific AEs (such as the high rate of diarrhoea in the small intestine group) that might be missed by an aggregated approach. Such differences in AE profiles across sites therefore need to be considered by the committee, because they highlight relatively high prevalence of adverse events in certain sites. Given that the

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		Hypothyroidism and hyperthyroidism were the most frequently reported AEOSI (≥3 participants) across all tumour sites (except for biliary and small intestine cancers where no AEOSI was reported for more than 2 participants). These are also generally consistent with the well-known safety profile of pembrolizumab monotherapy. Overall, these safety results from the KEYNOTE-158 trial demonstrate that pembrolizumab is well tolerated in participants with dMMR or MSI-H tumours across the four tumour sites.	committee will see the site-specific AEs, and will therefore be fully aware of the relatively high prevalence of certain events at certain sites, this issue is regarded by the EAG as resolved.
Issue 4: Mismatch in MSI-H/dMMR status between pembrolizumab population and comparator population.	Yes	**dMMR/MSI-H is considered a relevant predictive biomarker of response to pembrolizumab in the five tumour types relevant to this appraisal.** **This is supported by evidence from a number of studies stratified by MSI status that is suggestive of the increased activity of pembrolizumab in MSI-H patients relative to non MSI-H cancers.** **dMMR/MSI-H patients are not expected to respond better to chemotherapy than pMMR/MSS patients (i.e., MSI status is likely to be a negative prognostic factor) and therefore it is unlikely the ICERs would be higher (but may be potentially lower) if comparisons were performed in the dMMR/MSI-H comparator population.** For the five tumour types relevant to this appraisal, dMMR/MSI-H is considered a relevant predictive biomarker of response to pembrolizumab.	There is a mismatch in dMMR/MSI-H status between the pembrolizumab and comparator arms, which could create bias. The evidence cited by the company in the column on the left does, to some extent, support their belief that any bias would be conservative; that is, that it would diminish, rather than exaggerate, the apparent superiority of pembrolizumab. However, it is unclear if the evidence cited by the company covers all relevant data, or if the evidence itself is biased. Until a rigorously conducted systematic review on this topic is conducted, it is not possible to state the likely direction of bias with any degree of confidence. Therefore, the EAG would recommend that the committee maintain some scepticism about the company's claim that any bias resulting from the

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		This is supported by opinion of clinical experts who emphasised the role of **MSI-H as treatment effect modifier in relation to treatment with checkpoint inhibitors like pembrolizumab in these tumour sites**. (9) Previous studies had found that there was a dramatic overexpression of immune checkpoint-related proteins in the microenvironment of MSI CRC tumours, suggesting that immunotherapeutic interventions involving checkpoint blockade might be selectively effective in this subset of cancers. (10) This is also supported by a number of studies that include MSI-H patients and allow a within-study visual comparison of efficacy outcomes between MSI-H and non-MSI-H subgroups. • In the KEYNOTE-061 study, an RCT comparing pembrolizumab with paclitaxel in participants with advanced gastric /gastroesophageal junction adenocarcinoma that progressed after therapy with platinum and fluoropyrimidine, MSI-H gastric cancer patients treated with pembrolizumab had longer PFS and OS compared to chemotherapy; (11) also, a visual comparison of efficacy evidence between the MSI-H and non-MSI-H subgroups is suggestive of the increased activity of pembrolizumab in MSI-H advanced gastric cancer patients relative to non MSI-H cancer patients (median PFS of 17.8 vs 1.5 months and median OS not being reached vs 6.5 months in MSI-H and non-MSI-H subgroups, respectively) (Table 19 and Figure 1Figure 2). While the small number of patients in the MSI-H group may limit the interpretation of the findings, the baseline	mismatch in dMMR/MSI-H would be conservative. This issue is not resolved.

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		characteristics of the two subgroups are overall comparable (Table 20). • The ZEBRA study, a Phase 2 multicentre study of pembrolizumab in 40 patients with previously treated small-bowel adenocarcinoma, offers additional support for the predictive value of MSI-H. (12) The study was not biomarker-restricted but did stratify by MSI-H. The non-MSI-H participants had an ORR of only 8% with median PFS of 2.8 months and median OS of 6.6 months; in contrast, the ORR in MSI-H participants was 50% with median PFS and OS not being reached, though based on only 4 participants (Table 21). This is consistent with the ORR of 55.0% observed in the KEYNOTE-158 trial and highlights the significant activity of pembrolizumab in MSI-H small intestine tumours. • In the KEYNOTE-158 trial, 104 non-MSI-H patients with advanced biliary cancer treated with pembrolizumab within a different cohort had an ORR of 5.8% (2.1- 12.1) as opposed to 40.9% (20.7, 63.6) for MSI-H biliary cancer patients in cohort K (the cohort relevant to this appraisal). (13) Also, PFS and OS were shorter than in MSI-H patients (median PFS of 4.2 vs 2.0 months and median OS 19.4 vs 7.4 months in MSI-H and non-MSI-H cohorts, respectively) (Table 22). This represents further evidence of the positive predictive value of the MSI status for the approved indications. In addition to the evidence provided in the company submission about the prognostic value of MSI status, further evidence from the systematic literature review (SLR) suggests	

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		that **dMMR/MSI-H patients that are treated with chemotherapy are likely to have worse (or at least similar) prognosis than pMMR/MSS patients**. • In the KEYNOTE-775 trial, the evidence source used in the MAIC for the relevant comparators in endometrial cancer (paclitaxel or doxorubicin), randomisation was stratified according to MMR status. (14) While ORR and PFS are overall similar in dMMR and pMMR chemotherapy participants, OS findings suggest worse survival outcomes for dMMR patients with a median OS of 8.6 (5.5 – 12.9) for the dMMR subgroup vs 12.0 (10.8 – 13.3) for pMMR participants (Table 24); at 12 months, OS rate for the dMMR subgroup was 39.1% while nearly 50% of pMMR participants were still alive at 12 months (Figure 3Figure 4). Baseline characteristics of the two subgroups are presented in Table 25. • In addition to KEYNOTE-775, the SLR conducted for endometrial cancer identified McMeekin 2015 in which the comparator was paclitaxel or doxorubicin. This study was a Phase III randomized trial evaluating second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer with at least one failed prior platinum-based chemotherapeutic regimen. (15) Median age in the paclitaxel or doxorubicin group was 64 (33-88), similarly to dMMR population in KEYNOTE-775 (63.0) and the majority of patients were White whereas no baseline data were reported about ECOG PS and number of prior lines of therapy, which limit the comparison between the two groups. While the MSI/MMR status in the study population is unknown (i.e., unselected population), response and survival outcomes for the paclitaxel or doxorubicin group in the McMeekin 2015 study show	

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		better results compared to the dMMR chemotherapy population in KEYNOTE-775 (ORR 15.7% vs 12%; median OS 12.3 [10.7–15.4] vs 8.6 [5.5 – 12.9]) (Table 26). In contrast, the results in the paclitaxel or doxorubicin group in the McMeekin 2015 study are similar to all patients group in KEYNOTE-775 (Table 26). • In KEYNOTE-061 (gastric cancer), a naïve comparison of efficacy outcomes between MSI-H and non-MSI-H paclitaxel subgroups suggests similar prognosis (Table 19). Based on the above, it is reasonable to assume that ICERs would most likely not be higher if comparisons were performed in the MSI-H/dMMR comparator population. While acknowledging the limitations of the evidence above (e.g., lack of formal statistical comparison), this evidence certainly highlights a continued unmet need based on the clinical outcomes observed for the current standard of care in patients with MSI-H/dMMR cancers for these tumour types. This unmet need could be addressed with the availability of a more effective treatment such as pembrolizumab.	
Issue 5: High risk of bias in comparative efficacy.	Yes	**Relative effectiveness is not particularly biased compared to other later line solid-tumour indications and results remain highly cost-effective under alternative approaches, extreme treatment waning and exploratory worst-case extrapolation scenarios.** The relative treatment comparisons are potentially biased to the extent that both KEYNOTE-164 and KEYNOTE-158 are single-arm trials, but this is not uncommon in solid tumour	The fact remains that the base case uses non-randomised data that is not adjusted for confounding. The company's response does not in any way nullify this fact. Therefore, the EAG would continue to state that there is a high risk of bias in comparative efficacy. The EAG appreciates the company's effort of exploring different scenario analyses.

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		indications. In addition, comparator source OS/PFS KM (Kaplan–Meier) curves are fully mature which reduces uncertainty (i.e., virtually all patients are dead in the observed period). As acknowledged by the EAG, relative treatment effects were explored in the company submission via naïve ITCs, MAICs (where possible) and fitting independent parametric models (PSMs) to comparator evidence sources. The latter was selected in the base-case based on the violation of proportional hazards assumption; however, results remain cost-effective under all approaches. The EAG adopt the non-responder analyses for exploratory purposes (with curve selection based on best fits), which use pembrolizumab non-responders to reflect comparator efficacy. It should be noted that this is a conservative approach given that it involves fitting PSMs to data for patients from KEYNOTE-158 and KEYNOTE-164 who did not respond to 2L+ treatment with pembrolizumab (i.e., did not achieve complete or partial response). These will tend to be worst-case patients in a 3L+ setting who do not fit the license population. It is true that they are some subsets of the trial dataset used to model pembrolizumab efficacy and so there will be some control for confounders (i.e. within study or before and after type analysis); but this is only the case for time-constant and not time-variant factors (e.g. comorbidity status, change in fitness, new line of treatment). However, MSD agree this can be a useful worst-case exploratory scenario.	Although these analyses provide an indication of how sensitive the cost-effectiveness results are to choices in approach (BHM or PSM), the base-case and scenarios remain informed by non-randomised data that is not adjusted for confounding, as stated above and therefore risk of bias remains. This issue remains unresolved.

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		Under EAG settings (which reflect significant waning) and extreme exploratory worst-case scenarios all pairwise comparisons, weighted within tumour site results and overall indication results remain cost-effective (see Table 2 in sensitivity analysis results below):
		• Extreme treatment effect waning: waning from 7 to 9 years (from start of treatment) was included in the company base-case but also carried over to the EAG base-case and as explained previously the impact of this is considered clinically implausible but was included to reflect how cost-effective pembrolizumab remains:
		  ○ Plotted hazard functions for pembrolizumab over the duration of the trials (> 5 years) showed no evidence of treatment waning as patients finish pembrolizumab treatment (in-line with previous pembrolizumab trials).
		  ○ The plots below show that particularly for the 3 smaller sites (gastric, small intestine, biliary) there is an unrealistic drop in survival projections, which is highly conservative and inconsistent with clinical opinion.
		  ○ Waning is counter-intuitive in this case given that virtually all patients are dead in the chemotherapy comparators we wane against and this may explain the irregular impact on pembrolizumab survival.
		• Scenario A: shows non-responder analysis for comparators (in line with EAG exploratory analysis) as a worst-case scenario.	

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		• Scenario B: BHM (Bayesian hierarchical model) curve selections and PSM comparator curve selections that give the worst ICERs.
		  ○ These selections minimise (maximise) overall and progression-free state accrued QALYs for pembrolizumab (comparators). Comparator PSM selections do not drive results given the maturity of KMs. The Gompertz is now the BHM selection for all pembrolizumab OS/PFS curves, which was rejected by clinicians as too pessimistic (and does not have the best fit statistics).
		• Scenario C: This is the same as B but now the piecewise BHM for PFS is selected, this tends to have a better visual fit as discussed in the response to clarification questions.
		  ○ Both standard parametric survival models (PSMs) and BHM models did not fit the initial drop in PFS well. The drop is likely related to the first on-study imaging time point being performed at 9 weeks in both KEYNOTE-164 and KEYNOTE-158.
		• Scenario E: This scenario employs standard PSMs for pembrolizumab (based on a balance of fit statistics and previous clinical validations as explained in the response to clarification); these give improved ICERs compared to scenarios A to C.
		<u>Extreme impact of treatment waning on pembrolizumab survival (Gastric and small intestine sites)</u>	

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		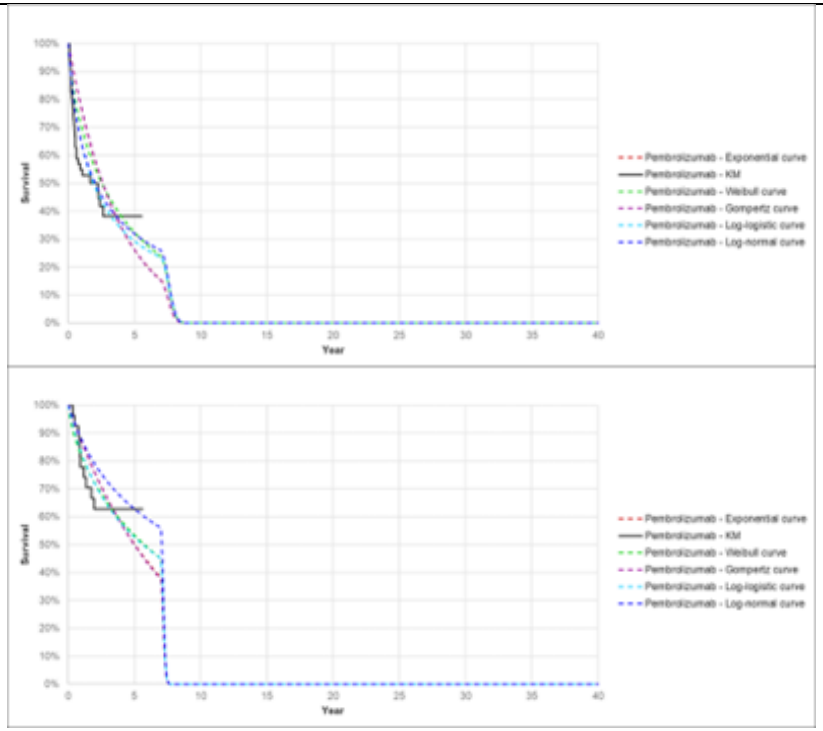	
Issue 6: Populations were aggregated across all tumour sites based on their MSI-H/dMMR status. However,	No	**This issue is considered resolved following technical engagement, given that pembrolizumab is consistently cost-effectiveness in all individual pairwise comparisons (and so by definition cost-effective in all aggregated results).** The cost-effectiveness of pembrolizumab vs. each individual chemotherapy comparator in any tumour site is accessible in the model and presented in the results and scenarios below.	No compelling new arguments or evidence provided. Hence, the EAG perspective as described in the EAG report remains unchanged.

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MSI-H/dMMR status for most comparators was unknown and heterogeneity between tumour sites seems substantial.		"Aggregation" here refers to the weighted averaging of these individual pairwise lifetime model outputs (total costs, total QALYs and ICERs) to produce cost-effectiveness results by tumour site and further to this for the overall indication. The weightings for aggregating comparator results within a tumour site were based on clinician estimates of market share; the aggregating of these further into overall indication results were based on either tumour site proportions from the trial or epidemiological calculations. Results are cost-effective for all pairwise comparisons and so by definition all aggregated results indicate cost-effectiveness – weighting calculations therefore are not a key technical issue that determines cost-effectiveness. Additionally, there is remarkable similarity in outcomes across the traditional chemotherapy comparators in all tumour sites: virtually all patients are dead by 4 years and accrued lifetime QALYs are consistently around 1. Lifetime accrued costs are also remarkably similar across chemotherapy comparators. This is different to assumptions about the heterogeneity of pembrolizumab efficacy between tumour sites and how different methods for extrapolating pembrolizumab OS/PFS make different assumptions about heterogeneity (issue 9).	
Issue 7: Treatment baskets were used to inform standard of care	No	**This issue is considered resolved following technical engagement and has no significant impact on cost-effectiveness.**	No compelling new arguments or evidence provided. The EAG considers this issue to be resolved given that fully incremental analyses for all tumour site are provided.

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per tumour site, which may bias the costs and outcomes of standard of care in the economic model.		To clarify, there are no baskets of costed treatments but final model lifetime cost-effectiveness results (e.g. lifetime accrued costs, QALYs, ICERs) for each pairwise comparison and these are aggregated as described above. When multiple sources of OS/PFS data for a given comparator (in a given tumour site) were identified these KM curves were usually pooled. For example, the abundance of source studies for 2L+ FOLFIRI/FOLFOX in CRC was a challenge; in this case different combinations of sources were compared side-by-side in the response to clarification questions and it was clear that efficacy did not vary significantly. MSD is indifferent about presenting results fully incrementally; however, for ease of interpretation results below are presented in pairwise fashion (pembrolizumab vs comparator).	
Issue 8: The selection of patients in the comparator studies was not based on their MSI-H/dMMR status, which introduced (methodological) uncertainty in	Yes	**The lack of available chemotherapy comparator data from sources that select patients based on dMMR/MSI-H status is unlikely to have a significant impact on cost-effectiveness and may even produce conservative cost-effectiveness results.** dMMR/MSI-H selected sources were only available for the paclitaxel in Gastric and TPC (paclitaxel/doxorubicin) in endometrial pairwise comparisons. Available evidence suggests that dMMR/MSI-H status is potentially a negative prognostic factor (see response to issue 4 above) and so results for chemotherapies with evidence from unselected	As stated in response to issue 4 above, it is unclear if the company's evidence suggesting that dMMR/MSI-H status is potentially a negative prognostic factor covers all relevant data, or if the evidence itself is biased. Therefore, the EAG would recommend that the committee maintain some scepticism about the company's claim that any bias resulting from the mismatch in dMMR/MSI-H would be conservative. The EAG appreciates the company's exploratory best/worst case scenario

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the estimation of the relative effectiveness of pembrolizumab.		sources may be slightly too optimistic (and ICERs higher than they otherwise would be). As explained in the technical engagement call, there is no error in the non-responder analysis; pembrolizumab arm results change with comparator curve fittings in any analysis when the waning functionality is on. In exploratory scenario analyses that can be considered the best case for chemotherapy comparators and worst case for pembrolizumab, results show consistent cost-effectiveness. See response to issue 5 above and the exploratory scenario results below (Table 2).	analyses and agrees that these can be useful to explore the impact of selecting pessimistic intervention curves and optimistic comparator curves on the cost-effectiveness results. Nevertheless, more detail on the company's assessment of the NICE DSU TSD 14 criteria for selecting these curves would be desirable.
Issue 9: The suitability of the Bayesian hierarchical model approach in the context of this submission was questionable.	Yes	**The "true" ICERs are somewhere around the BHM approach (assumes neither complete heterogeneity or homogeneity in pembrolizumab efficacy between tumour sites) and standard parametric models (PSMs) that assume complete heterogeneity. Pembrolizumab is consistently cost-effective across all approaches, extreme waning, and worst-case scenarios which limits the impact of uncertainty arising from this issue.** A method that pooled all pembrolizumab PFS/OS data irrespective of tumour site and so assumed complete homogeneity between all 5 tumour sites in KEYNOTE-164 (CRC) and KEYNOTE-158 (endometrial, gastric, small intestine, biliary) was never presented. Instead a Bayesian hierarchical model (BHM) and standard PSM approach was used to extrapolate the 5+ years of KM data:	The EAG would like to repeat that the BHM approach would only be appropriate if the assumption that the different tumour sites can be considered subgroups of an overarching MSI-H/dMMR solid tumour population is justified. The EAG acknowledges the advantage of the BHM approach allowing information to be borrowed between tumour sites, given their small individual sample sizes. However, considering the observed differences in terms of survival outcomes (OS, PFS), there seems to be substantial heterogeneity between the individual tumour sites. By applying BHM, tumour site-specific survival estimates are pulled to an overall average, which biases the survival estimates on individual tumour site

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		• BHMs: This is a multilevel model that assumes some exchangeability in efficacy between tumour sites, the greater the differences in PFS/OS between sites the greater the exchangeability.
		  ○ This is a middle ground between assuming complete homogeneity in pembrolizumab efficacy between sites (naive pooling) and complete heterogeneity (fitting separate PSM models as though sites are independent trials).
		  ○ This is the first appraisal where the BHM is used directly on survival outcomes; due to data limitations the NTRK tumour agnostic appraisals used the BHM applied only to response outcomes (then used these to weight survival curves).
		  ○ The model used was that suggested by the York EAG in the NTRK appraisals. The rate/scale/location parameter of a given survival distribution is a function of tumour site level random effects that vary by tumour site membership (as well as other standard fixed effects).
		• PSMs: These are the standard parametric models used in most oncology appraisals and in this context assume perfect heterogeneity in pembrolizumab efficacy across tumour sites (i.e., all tumour sites are assumed independent trials with no modelled MSI-H class effect).
		
		In the BHM approach, the model is fit across all five tumour sites (i.e., including the CRC dataset from KEYNOTE-164).
			level. Nevertheless, modelling of individual tumour sites using small sample sizes likely also introduces bias.
			
			Although the company did not provide the EAG's requested additional justification (supported by clinical arguments and evidence) regarding the assumption that the different tumour sites can be considered subgroups of an overarching MSI-H/dMMR solid tumour population, the company's scenario analyses (1. applying BHM to the four KEYNOTE-158 sites and a standard parametric curve to the CRC site in the pembrolizumab arm, and 2. applying standard parametric curves to all tumour sites in the pembrolizumab arm) had only a minor impact on the cost-effectiveness results. Hence, the choice of survival modelling approach is likely not a key model driver.

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		The EAG make the defensible point that it is inappropriate to include CRC in the BHM model given that it is a separate trial. However, a case can be made that it is reasonable to the extent that if CRC was included as a site in KEYNOTE-158, results would not differ systematically from results in KEYNOTE-164. This may be the case given that both trials are included in the same license: trial protocols are very similar, inclusion/exclusion criteria consistent, and sample size calculations suggest that a CRC site in KEYNOTE-158 would have a comparable sample size to KEYNOTE-164 (i.e., sample sizes are broadly proportional to incidence of the tumour type). Additional BHM models are time consuming to run and so as a compromise scenario the current BHM is applied to the four KEYNOTE-158 sites, with a standard PSM being applied to the CRC site. This makes very little difference to results as expected (Table 2; scenario D). As already explained in response to issue 5, even under worst-case scenarios pembrolizumab remains cost-effective (Table 2) which should limit uncertainty arising from this technical issue.	
Issue 10: The time-to-death utility approach to model the health-related quality of life of tumour sites included in KEYNOTE-158	No	**Pembrolizumab remains highly cost-effective under both the original time-to-death (TTD) and health state (HS) utility approaches for the KEYNOTE-158 sites, with HS now reflected in the updated base-case. However, the severity modifier is sensitive to this setting and all three smaller sites achieve the highest modifier weight under TTD (1.7) which makes pembrolizumab even more cost-effective.**	The EAG appreciates that the company aligned its base-case utility approach with the EAG's preferred health state-based approach. The EAG considers this issue to be resolved given that the EAG and company align on the approach for the estimation of utility values.

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was questionable.		KEYNOTE-164 (CRC) did not collect HRQoL data and so HS utilities are applied from the most conservative literature source (as agreed by the EAG). A TTD approach estimates utility weights based on the time from death category a patient falls into; in contrast to a HS approach that applies progression-free and progressed utilities. For the KEYNOTE-158 tumour sites (endometrial, gastric, small intestine, biliary) a TTD utility model was fitted to the whole sample (irrespective of tumour site status) given the small numbers of patients by tumour site in some TTD categories. The HS utility approach for KEYNOTE-158 was fitted to produce different utilities by tumour site. When presented with the methods, clinicians believed both were clinically plausible but there was a slight preference for TTD given that for immunotherapies there is a longer tail of survival irrespective of progression status (i.e., time from death can matter more than progression status). Very conservatively, the comparator chemotherapies in these KEYNOTE-158 sites are given these same pembrolizumab utilities in modelling. Under either approach pembrolizumab remains cost-effective – however the TTD utility approach gives lower ICERs and lower accrued QALYs for chemotherapy comparators and tips the gastric and small intestine sites into the highest severity modifier category:	

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		• Endometrial: under TTD the ICER is lower compared with HS (£15,126 vs £17,408). Severity modifier remains at 1.2. • Gastric: under TTD the ICER is lower compared with HS (£22,736 vs £26,548). Severity modifier also increases to 1.7, lowering the ICER further to £16,049. • Small intestine: under TTD the ICER is lower compared with HS (£21,774 vs £22,440). Severity modifier also increases to 1.7, lowering the ICER further to £15,370. • Biliary: under TTD the ICER is lower compared with HS (£13,657 vs £14,471). Severity modifier remains at 1.7.	
Issue 11: Assumptions regarding the modelling of subsequent treatments were questionable.	No	**This issue is considered resolved following technical engagement and has no significant impact on cost-effectiveness, because as expected most patients receive BSC at 3L+ in these metastatic cancers.** Subsequent treatment proportions from the KEYNOTE-164 and KEYNOTE-158 trials show that most patients will not receive subsequent treatments but BSC. Depending on tumour site the proportion varies from 60-80% receiving BSC. The proportions receiving subsequent treatments are as follows: 26.6% (CRC), 22.9% (endometrial), 19.6% (gastric), 40.7% (small intestine) and 33.3% (biliary). These high proportions on BSC are expected in the later line metastatic setting and clinicians broadly agreed with these proportions. For simplicity, it was assumed that comparator treatment arms in the model also received these same proportions and same treatments, and this was supported by clinicians. Accrued life-time subsequent treatment costs vary	Apart from the company's statement that the assumption of equal proportions of patients receiving subsequent treatments regardless of the initial line of therapy was based on simplicity and supported by clinicians (which the EAG did not observe to be reported by clinical experts in the advisory board minutes), no compelling new arguments or evidence to support this assumption were provided. In addition, the company did also not provide further justification or evidence regarding the generalisability of the modelled subsequent treatments to UK clinical practice. Hence, the EAG perspective as described in the EAG report remains unchanged.

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		slightly between pembrolizumab and comparator arms due to differences in progression rates. The reported subsequent treatments are composed of traditional chemotherapies and it is unclear how they might differ in practice between pembrolizumab and the comparators. For example, it is unlikely that patients in the comparator arms receive immunotherapies in these later lines but if they did this would reduce ICERs slightly (i.e., higher accrued subsequent treatment costs for comparators). Scenarios that double proportions of subsequent treatments or remove them entirely have been added to the model (bottom of Model Control sheet), but as expected these change the ICERs by around 1%.	
Issue 12: Testing costs to identify patients with MSI-H/dMMR were not included in the company's base-case analysis.	No	**This issue is considered resolved following technical engagement and has no significant impact on cost-effectiveness. There is some consensus that dMMR/MSI-H testing is uncertain and less well established in the smaller tumour sites (gastric, small intestine, biliary) and so 50% testing costs are assumed. Results remain cost-effective even when 100% testing costs are included in modelling.** There is a broad consensus that testing is established in the larger tumour sites (CRC, endometrial) based on clinician input and previous appraisals and so no additional testing costs are included in the model for these. The MSI-H test directory (UK genomics hubs) officially cover all five tumour sites in the full license related to this appraisal	The EAG appreciates that the company aligned its base-case testing costs with the EAG's base-case. The EAG considers this issue to be resolved given that the EAG and company align on the modelled testing costs to identify patients with MSI-H/dMMR. For completeness the EAG also explored the impact of assuming 100% testing costs in all tumour sites (including CRC and endometrial cancer). This had a larger but still minor impact on the weighted average and endometrial tumour site results, and a moderate impact (ICER increased by ± £2,500) on the CRC tumour site results.

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		(16). However, in clinical practice there is uncertainty about how established testing is for the three smaller sites (gastric, small intestine, biliary). As a compromise, 50% of testing costs are included in the updated base-case (Table 1). 100% testing costs are included in a scenario analysis, but this has little impact and pembrolizumab remains cost-effective in these sites (Table 3).	
Issue 13: Severity estimates were based on the company's modelling of QALYs, which was subject to limitations, and therefore uncertain.	No	**The EAG preference for severity modifiers is reflected in the updated base-case (all sites achieve a 1.2 multiplier, with biliary achieving the 1.7). However, it is important to emphasise that under plausible settings the gastric and small intestine sites achieve the highest 1.7 multiplier and this should be considered in decision making**. For all sites the comparator/SOC proportional QALY shortfall is well into the cut-offs for achieving at least a 1.2 severity modifier with updated base-case settings (>[redacted]%): [redacted]% (CRC), [redacted]% (endometrial), [redacted]% (gastric), [redacted]% (small intestine) and [redacted]% (biliary). There is agreement that the biliary site achieves the 1.7 modifier (proportional QALY shortfall is >95%), however it is important to emphasise how easy it is to tip the gastric and small intestine sites into this higher category. If you reduce accrued lifetime QALYs for the comparators in these sites by only 0.08 (i.e. 8% of a QALY) the highest severity modifier is achieved. There are several reasons why the model may overestimate accrued QALYs for these chemotherapy comparators and so	The EAG acknowledges the overall uncertainty in the severity estimates and appreciates that the company aligned its base-case severity modifiers with the EAG's base-case. The severity estimates are indeed sensitive to the selected utility approach, and current severity estimates (1.2 for all tumour sites but cholangiocarcinoma [1.7]) are in line with the EAG's preferred health state-based utility approach. The company's statement regarding the potential overestimation of comparator HRQoL for KEYNOTE-158 chemotherapy comparators should be supported by evidence. Finally, as stated in response to issues 4 and 8 above, it is unclear whether the company's evidence suggesting that dMMR/MSI-H status is potentially a negative prognostic factor is unbiased. Hence, it is currently not possible to state the likely direction of bias.

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		in reality gastric and small intestine may reach the cut-off for the highest severity modifier: • The modifiers are sensitive to the TTD vs. HS utility settings and under the TTD approach the gastric and small intestine sites achieve the 1.7 multiplier (see issue 10 above). • For the KEYNOTE-158 sites (all sites excluding CRC) the chemotherapy comparators are given pembrolizumab KEYNOTE-158 derived utilities and this will overestimate accrued QALYs for these comparators (especially in the progression free state as QoL is likely to be lower on chemotherapies). • MSI-H/dMMR status is potentially a negative prognostic factor for patients receiving these chemotherapies (see response to issue 4) and so for unselected comparator sources we may be overestimating survival and accrued QALYs (all comparators in CRC, small intestine and biliary and FOLFIRI in gastric).	
Issue 14: The majority of the company's scenario analyses could not be reproduced and lacked face validity.	Yes	**This issue is considered resolved following technical engagement and has no significant impact on cost-effectiveness.** MSD apologise that some scenario results in the company submission contained errors because of a typo in named ranges in the VBA code for the automated scenario functionality. This has been corrected (switch added at the bottom of Model Controls sheet) with automated scenario analyses results re-run in the updated model. The correction makes very little difference to scenario analysis results.	The EAG could verify the company's original scenario analyses results in its corrected economic model and hence considers this issue resolved.

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		In addition, MSD has corrected an error in the way administration costs were applied to oral therapies in the model – the HRG cost was applied per administration instead of as a one-off cost as appropriate. This has been corrected and for simplicity all oral admin costs are £0 now (see bottom of Model Controls sheet). This mainly impacts the TAS-102 comparison in CRC (the only oral administration comparator) and ICERs remain well below threshold levels.	

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Summary of changes to the company's cost-effectiveness estimate(s)

Table 1 is the updated base-case and is the same as the EAG base-case. Results are presented as pembrolizumab vs. comparator and are inclusive of pembrolizumab confidential PAS. Probabilistic ICERs are very similar (overall indication PSA ICER is £18,240). Key settings are as follows:

- The error for oral medication dosing is corrected (and oral admin costs set to £0) and this mainly impacts the TAS-102 (CRC) comparison (see response to issue 14 above)
- These include the QALY severity weightings endorsed by the EAG: 1.2 multiplier in all sites except biliary (1.7 multiplier)
- Health state (by site) utility approach instead of time-to-death utilities
- 50% testing costs are included for the 3 smaller tumour sites: gastric, endometrial, and biliary
- Using epidemiological calculations as the basis of tumour site weighting when deriving overall indication ICER

Table 1 Updated company base-case (EAG base-case inclusive of extreme treatment effect waning from company base-case)

		Pairwise ICERs	Weighted tumour site ICER
Overall indication deterministic ICER:		£18,549	
Colorectal	TAS-102	£13,413	£13,783
	Pooled FOLFOX/FOLFIRI	£13,962	
Endometrial	Paclitaxel	£16,395	£17,408
	Doxorubicin	£17,914	
Gastric	Paclitaxel	£26,166	£26,548
	FOLFIRI	£27,387	

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Small intenstine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£22,440	£22,440
Biliary (cholangiocarcinoma)	mFOLFOX	£14,374	£14,471
	mFOLFIRI	£15,330	

Sensitivity analyses around revised base case

The results below reflect EAG settings as described above but with additional exploratory worst-case settings (see response to issue 5 above). Note that B is pre-programmed into the scenario selection functionality on the Model Controls sheet; scenario C is the same as B but PFS selections are then switched to piecewise BHM models (same functions); and D is the "naive PSM" scenario in scenario selection (but EAG settings and waning must be re-inputted again).

Table 2 EAG base-case but with additional exploratory and extreme worst-case scenario results

			Pairwise ICERs	**Weighted tumour site ICER**
A: Pembrolizumab Non-responder analysis	**Overall indication ICER:**		£22,382	
	Colorectal	TAS-102	£20,978	£19,981
		Pooled FOLFOX/FOLFIRI	£19,554	
	Endometrial	Paclitaxel	£24,080	£26,053
		Doxorubicin	£27,040	
	Gastric	Paclitaxel	£24,774	£24,662
		FOLFIRI	£24,402	
	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£20,347	£20,347
	Biliary (cholangiocarcinoma)	mFOLFOX	£14,136	£14,250
		mFOLFIRI	£15,271	
	Overall indication ICER:		£22,879	

B: Worst case (pessimistic) pembrolizumab curve selections and best case (optimistic) comparator selections	**Colorectal**	TAS-102	£17,811	£18,536
		Pooled FOLFOX/FOLFIRI	£18,892	
	Endometrial	Paclitaxel	£20,016	£24,366
		Doxorubicin	£27,160	
	Gastric	Paclitaxel	£26,887	£27,408
		FOLFIRI	£28,642	
	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£25,168	£25,168
	Biliary (cholangiocarcinoma)	mFOLFOX	£15,368	£15,507
		mFOLFIRI	£16,777	
C: analysis B but with worst case piecewise for pembrolizumab PFS	**Overall indication ICER:**		£22,912	
	Colorectal	TAS-102	£16,653	£17,243
		Pooled FOLFOX/FOLFIRI	£17,531	
	Endometrial	Paclitaxel	£20,081	£24,345
		Doxorubicin	£27,069	
	Gastric	Paclitaxel	£28,176	£28,698
		FOLFIRI	£29,935	
	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£26,547	£26,547
	Biliary (cholangiocarcinoma)	mFOLFOX	£14,893	£15,029
		mFOLFIRI	£16,268	
D: PSM for pembrolizumab in CRC; remaining sites BHM	**Overall indication ICER:**		£18,553	
	Colorectal	TAS-102	£13,354	£13,724
		Pooled FOLFOX/FOLFIRI	£13,904	
	Endometrial	Paclitaxel	£16,395	£17,408
		Doxorubicin	£17,914	
	Gastric	Paclitaxel	£26,166	£26,548
		FOLFIRI	£27,387	

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	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£22,440	£22,440
	Biliary (cholangiocarcinoma)	mFOLFOX	£14,374	£14,471
		mFOLFIRI	£15,330	
E: PSMs for pembrolizumab (best fit and clinically plausible)	**Overall indication ICER:**		£19,143	
	Colorectal	TAS-102	£13,354	£13,724
		Pooled FOLFOX/FOLFIRI	£13,904	
	Endometrial	Paclitaxel	£15,913	£16,871
		Doxorubicin	£17,350	
	Gastric	Paclitaxel	£28,138	£28,508
		FOLFIRI	£29,316	
	Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£25,908	£25,908
	Biliary (cholangiocarcinoma)	mFOLFOX	£17,005	£17,117
		mFOLFIRI	£18,109	

Table 3 EAG base-case but with 100% testing costs accrued in gastric, small intestine and biliary

		Pairwise ICERs	**Weighted tumour site ICER**
Overall indication ICER:		£18,803	
Colorectal	TAS-102	£13,413	£13,783
	Pooled FOLFOX/FOLFIRI	£13,962	
Endometrial	Paclitaxel	£16,395	£17,408
	Doxorubicin	£17,914	
Gastric	Paclitaxel	£26,761	£27,133
	FOLFIRI	£27,948	
Small intestine	Nab-paclitaxel (proxy for FOLFOX/FOLFIRI)	£22,902	£22,902

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Biliary (cholangiocarcinoma)	mFOLFOX	£15,680	£15,775
	mFOLFIRI	£16,618	

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APPENDIX A

Issue 2

KEYNOTE-164 (CRC)

Table 4 ORR by race group based on IRC Assessment per RECIST 1.1 (ASaT Population) (KEYNOTE-164, CRC)

		Objective Response (CR+PR)
	n	% (95% CI†)
All	42	33.9 (25.6; 42.9)
White	27	[redacted]
Non-White	15	
Asian	11	
Only confirmed responses are included (n=42) † Based on binomial exact confidence interval method. Database Cutoff Date: 19FEB2021		

Abbreviations: ASaT, all subjects as treated population; CR, complete response; PR, partial response
Notes: Non-White subgroup includes Asian (n=11) and Black Or African American (n=4)

Table 5 Summary of Progression-Free Survival (PFS) Based on IRC Assessment per RECIST 1.1 (ASaT Population) (KEYNOTE-164, CRC)

	White	Non-White	Asian
Subjects in population	84	40	33

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Number (%) of PFS Events	[redacted]	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]	[redacted]
Median PFS (Months)§	[redacted]	[redacted]	[redacted]
95% CI for Median PFS§	[redacted]	[redacted]	[redacted]
PFS rate at 6 Months in % §	[redacted]	[redacted]	[redacted]
PFS rate at 12 Months in % §	[redacted]	[redacted]	[redacted]
PFS rate at 24 Months in % §	[redacted]	[redacted]	[redacted]
PFS rate at 36 Months in % §	[redacted]	[redacted]	[redacted]
Progression-free survival is defined as time from first day of study treatment to disease progression, or death, whichever occurs first. § From product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 19FEB2021			

Abbreviations: ASaT, all subjects as treated population; PFS, progression-free survival
Notes: Non-White subgroup includes Asian (n=33) and Black Or African American (n=7)

Table 6 Summary of Overall Survival (ASaT Population) (KEYNOTE-164, CRC)

	White	Non-White	Asian
Subjects in population	84	40	33

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Number (%) of Events	[redacted]	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]	[redacted]
Median OS (Months)§	[redacted]	[redacted]	[redacted]
95% CI for Median OS§	[redacted]	[redacted]	[redacted]
OS rate at 12 Months in % §	[redacted]	[redacted]	[redacted]
OS rate at 24 Months in % §	[redacted]	[redacted]	[redacted]
OS rate at 36 Months in % §	[redacted]	[redacted]	[redacted]
OS rate at 48 Months in % §	[redacted]	[redacted]	[redacted]
§ From product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 19FEB2021			

Abbreviations: ASaT, all subjects as treated population; OS, overall survival
Notes: Non-white subgroup includes Asian (n=33) and Black Or African American (n=7)

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KEYNOTE-158

Objective Response rate (ORR)

Table 7 Summary of Best Objective Response Based on RECIST1.1 per Central Radiology Assessment (ASaT Population in Cohort K)

Gastric cancer

Response Evaluation	White (N=32)			Asian (N=14)			Other (N=5)		
	n	%	95% CI[a]	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)									
Partial Response (PR)									
Objective Response (CR+PR)									
Stable Disease (SD)									
Progressive Disease (PD)									

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Non-evaluable (NE)									
No Assessment									

Endometrial cancer

Response Evaluation	White (N=70)			Non-White (N=11)		
	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)						
Partial Response (PR)						
Objective Response (CR+PR)						
Stable Disease (SD)						
Progressive Disease (PD)						
Non-evaluable (NE)						
No Assessment						

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Participants with missing race are not included.						

Biliary cancer

Response Evaluation	White (N=20)			Non-White (N=2)		
	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)						
Partial Response (PR)						
Objective Response (CR+PR)						
Stable Disease (SD)						
Progressive Disease (PD)						
No Assessment						

Small Intestine Cancer

Response Evaluation	White (N=22)			Non-White (N=5)		
	n	%	95% CI[a]	n	%	95% CI[a]
Complete Response (CR)						
Partial Response (PR)						

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Objective Response (CR+PR)	
Stable Disease (SD)	
Progressive Disease (PD)	
No Assessment	

[a] Based on binomial exact confidence interval method.
Notes: Central radiology assessed responses per RECIST 1.1 (confirmed) are included in this table.
'No Assessment' (NA) counts subjects who had a baseline assessment evaluated by the central radiology assessment but no post-baseline assessment on the data cutoff date including missing, discontinuing or death before the first post-baseline scan.
Database Cutoff Date: 12JAN2022

Progression-free Survival (PFS)

Table 8 Summary of Progression-Free Survival (PFS) Based on RECIST 1.1 per Central Radiology Assessment (ASaT Population in Cohort K)

Gastric Cancer

	White (N=32)	Asian (N=14)	Other (N=5)
Number (%) of PFS Events			
Person-Months			
Event Rate/100 Person-Months			

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(%)	[redacted]	[redacted]	[redacted]
Median PFS (Months)[a]	[redacted]	[redacted]	[redacted]
95% CI for Median PFS[a]	[redacted]	[redacted]	[redacted]
PFS rate at 6 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 12 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 24 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 36 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 48 Months in % [a]	[redacted]	[redacted]	[redacted]
PFS rate at 60 Months in % [a]	[redacted]	[redacted]	[redacted]

Endometrial Cancer

	White	Non-White

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	(N=70)	(N=11)
Number (%) of PFS Events	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]
Median PFS (Months)[a]	[redacted]	[redacted]
95% CI for Median PFS[a]	[redacted]	[redacted]
PFS rate at 6 Months in % [a]	[redacted]	[redacted]
PFS rate at 12 Months in % [a]	[redacted]	[redacted]
PFS rate at 24 Months in % [a]	[redacted]	[redacted]
PFS rate at 36 Months in % [a]	[redacted]	[redacted]
PFS rate at 48 Months in % [a]	[redacted]	[redacted]

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PFS rate at 60 Months in % [a]	[redacted]	[redacted]
Participants with missing race are not included.		

Biliary Cancer

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	White (N=20)	Non-White (N=2)
Number (%) of PFS Events	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]
Median PFS (Months)[a]	[redacted]	[redacted]
95% CI for Median PFS[a]	[redacted]	[redacted]
PFS rate at 6 Months in % [a]	[redacted]	[redacted]
PFS rate at 12 Months in % [a]	[redacted]	[redacted]
PFS rate at 24 Months in % [a]	[redacted]	[redacted]
PFS rate at 36 Months in % [a]	[redacted]	[redacted]
PFS rate at 48 Months in % [a]	[redacted]	[redacted]

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PFS rate at 60 Months in % [a]	[redacted]	[redacted]

Small Intestine Cancer

	White (N=22)	Non-White (N=5)
Number (%) of PFS Events	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]
Event Rate/100 Person-Months (%)	[redacted]	[redacted]
Median PFS (Months)[a]	[redacted]	[redacted]
95% CI for Median PFS[a]	[redacted]	[redacted]
PFS rate at 6 Months in % [a]	[redacted]	[redacted]

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PFS rate at 12 Months in % [a]	[redacted]	[redacted]
PFS rate at 24 Months in % [a]	[redacted]	[redacted]
PFS rate at 36 Months in % [a]	[redacted]	[redacted]
PFS rate at 48 Months in % [a]	[redacted]	[redacted]
PFS rate at 60 Months in % [a]	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.
Notes: Progression-free survival is defined as time from date of first dose to disease progression, or death, whichever occurs first.
Abbreviations: NR, Not reached; PFS, progression-free survival
Database Cutoff Date: 12JAN2022

Overall Survival (OS)

Table 9 Summary of Overall Survival (ASaT Population in Cohort K)

Gastric Cancer

	White (N=32)	Asian (N=14)	Other (N=5)
Death (%)	[redacted]	[redacted]	[redacted]

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Median Survival (Months)[a]				Endometrial Cancer
95% CI for Median Survival[a]				
OS rate at 6 Months in % [a]				
OS rate at 12 Months in % [a]				
OS rate at 24 Months in % [a]				
OS rate at 36 Months in % [a]				
OS rate at 48 Months in % [a]				
Death (%)				
OS rate at 60 Months in % [a]				
Median Survival (Months)[a]				
OS rate at 72 Months in % [a]				
95% CI for Median Survival[a]				
OS rate at 6 Months in % [a]				
OS rate at 12 Months in % [a]				
OS rate at 24 Months in % [a]				

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OS rate at 36 Months in % [a]	[redacted]	[redacted]
OS rate at 48 Months in % [a]	[redacted]	[redacted]
OS rate at 60 Months in % [a]	[redacted]	[redacted]
OS rate at 72 Months in % [a]	[redacted]	[redacted]
Participants with missing race are not included		

Biliary Cancer

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	White (N=20)	Non-White (N=2)
Death (%)	[redacted]	[redacted]
Median Survival (Months)[a]	[redacted]	[redacted]
95% CI for Median Survival[a]	[redacted]	[redacted]
OS rate at 6 Months in % [a]	[redacted]	[redacted]
OS rate at 12 Months in % [a]	[redacted]	[redacted]
OS rate at 24 Months in % [a]	[redacted]	[redacted]
OS rate at 36 Months in % [a]	[redacted]	[redacted]
OS rate at 48 Months in % [a]	[redacted]	[redacted]
OS rate at 60 Months in % [a]	[redacted]	[redacted]
OS rate at 72 Months in % [a]	[redacted]	[redacted]

Technical engagement response form

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Small Intestine Cancer

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	White (N=22)	Non-White (N=5)
Death (%)	[redacted]	[redacted]
Median Survival (Months)[a]	[redacted]	[redacted]
95% CI for Median Survival[a]	[redacted]	[redacted]
OS rate at 6 Months in % [a]	[redacted]	[redacted]
OS rate at 12 Months in % [a]	[redacted]	[redacted]
OS rate at 24 Months in % [a]	[redacted]	[redacted]
OS rate at 36 Months in % [a]	[redacted]	[redacted]
OS rate at 48 Months in % [a]	[redacted]	[redacted]
OS rate at 60 Months in % [a]	[redacted]	[redacted]
OS rate at 72 Months in % [a]	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.
Abbreviations: NR, Not reached; OS, overall survival
Database Cutoff Date: 12JAN2022

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Issue 3

Table 10 Adverse Event Summary - Participants: MSI-H with Gastric, Endometrial, Biliary and Small Intestine Cancer (ASaT Population)

	Gastric		Endometrial		Biliary (cholangiocarcinoma)		Small intestine	
	Pembrolizumab 200 mg Q3W							
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	51		83		22		27	
with one or more adverse events	[redacted]							
with drug-related[a] adverse events	[redacted]							
with serious adverse events	[redacted]							
with serious drug-related adverse events	[redacted]							
with dose reduction due to an adverse event	[redacted]							
with dose reduction due to a drug-related adverse event	[redacted]							
who died	[redacted]							
who died due to a drug-related adverse event	[redacted]							
discontinued drug due to an adverse event	[redacted]							
discontinued drug due to a drug-related adverse event	[redacted]							

[a] Determined by the investigator to be related to the drug
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
Database Cutoff Date: 12JAN2022

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Gastric cancer

The most frequently reported AEs (incidence ≥20%) were diarrhoea, asthenia, fatigue, and arthralgia. Anaemia, abdominal pain, alanine transferase increased, and pruritus were reported with a frequency of 19.6%.

Table 11 Frequency and severity of adverse events according to the SOC classification- Participants: MSI-H with Gastric Cancer (All grade AE with Incidence ≥5% or Grade 3+ AE with Incidence ≥5%) (ASaT Population)

SOC rating/event	Pembrolizumab 200 mg Q3W n (%) Toxicity of all Grades	 n (%) Toxicity of Grade ≥ 3
Participants in population	51	51
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]

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Ear and labyrinth disorders	[redacted]	[redacted]
Endocrine disorders		
Hypothyroidism		
Eye disorders		
Gastrointestinal disorders		
Diarrhoea		
Abdominal pain		
Constipation		

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Vomiting	[redacted]	[redacted]	
Abdominal pain upper			
Nausea			
Ascites			
General disorders and administration site conditions			
Asthenia			
Fatigue			
Pyrexia			
Influenza like illness			
Malaise			

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Oedema peripheral	[redacted]	[redacted]
Hepatobiliary disorders		
Infections and infestations		
Rhinitis		
Injury, poisoning and procedural complications		
Investigations		
Alanine aminotransferase increased		
Aspartate aminotransferase increased		

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Blood alkaline phosphatase increased	[redacted]	[redacted]
Metabolism and nutrition disorders		
Decreased appetite		
Hyperkalaemia		
Hypoalbuminaemia		
Hyperglycaemia		
Hypokalaemia		
Musculoskeletal and connective tissue disorders		
Arthralgia		

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Back pain	[redacted]	[redacted]
Nervous system disorders		
Dizziness		
Dysgeusia		
Psychiatric disorders		
Renal and urinary disorders		
Respiratory, thoracic and mediastinal disorders		

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Dyspnoea	[redacted]	[redacted]
Oropharyngeal pain		
Skin and subcutaneous tissue disorders		
Pruritus		
Dry skin		
Vascular disorders		

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03 and MedDRA version is 24.1
Database Cutoff Date: 12JAN2022

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Table 12 Participants With Adverse Events by AEOSI Category and Preferred Term (Incidence > 0%) - Participants: MSI-H with Gastric Cancer (ASaT Population)

	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	51	
with one or more adverse events		
with no adverse events		
Colitis		
Colitis		
Guillain-Barre Syndrome		
Guillain-Barre syndrome		
Hepatitis		
Hepatitis		
Hyperthyroidism		
Hyperthyroidism		
Hypothyroidism		
Hypothyroidism		
Myocarditis		
Myocarditis		
Myositis		
Myopathy		
Nephritis		
Nephritis		
Tubulointerstitial nephritis		
Pneumonitis		
Interstitial lung disease		
Pneumonitis		

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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: 12JAN2022

Endometrial cancer

The most frequently reported AEs (incidence ≥20%) were diarrhoea, nausea, vomiting, fatigue, arthralgia, pruritus, urinary tract infection and decreased appetite.

Table 13 Frequency and severity of adverse events according to the SOC classification - Participants: MSI-H with Endometrial Cancer (All grade AE with Incidence ≥5% or Grade 3+ AE with Incidence ≥5%) (ASaT Population)

	Pembrolizumab 200mg Q3W			
	n	(%)	n	(%)

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SOC rating/event	Toxicity of all Grades	Toxicity of Grade ≥ 3
Participants in population	83	83
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]

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Eye disorders	[redacted]	[redacted]
Gastrointestinal disorders		
Diarrhoea		
Nausea		
Vomiting		
Constipation		
Abdominal pain		
Dry mouth		
General disorders and administration site conditions		

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Fatigue	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]

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Investigations	[redacted]	[redacted]
Aspartate aminotransferase increased		
Blood creatinine increased		
Alanine aminotransferase increased		
Lymphocyte count decreased		
Weight decreased		
Metabolism and nutrition disorders		
Decreased appetite		
Hypomagnesaemia		
Hyperglycaemia		

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Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]
Arthralgia			
Back pain			
Muscle spasms			
Myalgia			
Pain in extremity			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nervous system disorders			
Headache			

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Dizziness	[redacted]	[redacted]	
Neuropathy peripheral			
Psychiatric disorders			
Insomnia			
Anxiety			
Renal and urinary disorders			
Reproductive system and breast disorders			
Vaginal haemorrhage			

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Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]

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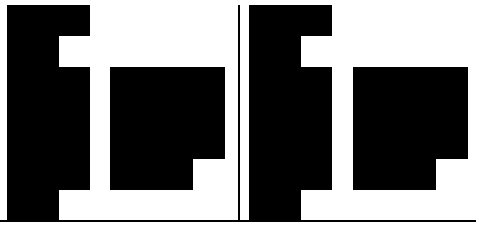
Hypertension		

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03 and MedDRA version is 24.1
Database Cutoff Date: 12JAN2022

Table 14 Participants With Adverse Events by AEOSI Category and Preferred Term (Incidence > 0%) - Participants: MSI-H with Endometrial Cancer (ASaT Population)

	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	83	
with one or more adverse events		
with no adverse events		
Colitis		
Colitis		
Enterocolitis		
Hyperthyroidism		
Hyperthyroidism		
Hypothyroidism		
Hypothyroidism		
Infusion Reactions		
Infusion related reaction		
Myositis		
Myositis		
Pneumonitis		
Pneumonitis		
Severe Skin Reactions		
Pemphigoid		
Rash		
Rash maculo-papular		
Type 1 Diabetes Mellitus		
Type 1 diabetes mellitus		
Uveitis		
Uveitis		

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Biliary cancer (Cholangiocarcinoma)

The most frequently reported AEs (incidence ≥20%, corresponding to approximately ≥4 study participants) were diarrhoea, abdominal pain, vomiting, constipation, fatigue, pyrexia, asthenia, alanine transferase increased, blood alkaline phosphatase increased and weight decreased.

Table 15 Frequency and severity of adverse events according to the SOC classification - Participants: MSI-H with Cholangiocarcinoma (All grade AE with Incidence ≥5% or Grade 3+ AE with Incidence ≥5%) (ASaT Population)

SOC rating/event	Pembrolizumab 200mg Q3W n (%) Toxicity of all Grades	 n (%) Toxicity of Grade ≥ 3
Participants in population	22	22
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]

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Cardiac disorders	[redacted]	[redacted]
Eye disorders		
Gastrointestinal disorders		
Diarrhoea		
Abdominal pain upper		
Vomiting		
Constipation		
Nausea		
Dyspepsia		

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General disorders and administration site conditions	[redacted]	[redacted]
Fatigue		
Pyrexia		
Asthenia		
Oedema peripheral		
Non-cardiac chest pain		
Hepatobiliary disorders		
Infections and infestations		
Nasopharyngitis		

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Influenza	[redacted]	[redacted]
Liver abscess	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Vascular device infection	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Rib fracture	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]

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Blood alkaline phosphatase increased	[redacted]
Weight decreased	
Aspartate aminotransferase increased	
Blood bilirubin increased	
Platelet count decreased	
Metabolism and nutrition disorders	
Decreased appetite	
Musculoskeletal and connective tissue disorders	
Arthralgia	

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Back pain	[redacted]	[redacted]
Muscle spasms		
Nervous system disorders		
Headache		
Psychiatric disorders		
Insomnia		
Respiratory, thoracic and mediastinal disorders		
Cough		
Epistaxis		

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Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash		
Pruritus		
Rash maculo-papular		

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03 and MedDRA version is 24.1
Database Cutoff Date: 12JAN2022

Table 16 Participants With Adverse Events by AEOSI Category and Preferred Term (Incidence > 0%) - Participants: MSI-H with Cholangiocarcinoma (ASaT Population)

	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	22	
with one or more adverse events	[redacted]	[redacted]
with no adverse events		
Hepatitis	[redacted]	[redacted]
Hepatitis		
Hypothyroidism		
Hypothyroidism		

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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: 12JAN2022

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Small Intestine Cancer

The most frequently reported AEs (incidence ≥20%, corresponding to approximately ≥5 study participants) were diarrhoea, abdominal pain, fatigue and pruritus.

Table 17 Frequency and severity of adverse events according to the SOC classification - Participants: MSI-H with Small Intestine Cancer (All grade AE with Incidence ≥5% or Grade 3+ AE with Incidence ≥5%) (ASaT Population)

SOC rating/event	Pembrolizumab 200mg Q3W n (%) Toxicity of all Grades	 n (%) Toxicity of Grade ≥ 3
Participants in population	27	27
with one or more adverse events	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]

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Palpitations	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders			
Vertigo	[redacted]	[redacted]	[redacted]
Endocrine disorders			
Hyperthyroidism	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]
Eye disorders			

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Gastrointestinal disorders	[redacted]	[redacted]	
Diarrhoea			
Abdominal pain			
Constipation			
Nausea			
Vomiting			
Dyspepsia			
Abdominal pain upper			
Dry mouth			
General disorders and administration site conditions			

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Fatigue	[redacted]	[redacted]	
Asthenia			
Pyrexia			
Influenza like illness			
Oedema peripheral			
Hepatobiliary disorders			
Hepatitis			
Infections and infestations			
Influenza			

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Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Tooth infection	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]

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Decreased appetite	[redacted]	[redacted]
Dehydration		
Musculoskeletal and connective tissue disorders		
Arthralgia		
Back pain		
Myalgia		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Nervous system disorders		
Headache		

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Dizziness	[redacted]	[redacted]
Psychiatric disorders		
Depression		
Insomnia		
Renal and urinary disorders		
Reproductive system and breast disorders		
Respiratory, thoracic and mediastinal disorders		

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Cough	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]	[redacted]

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included
MedDRA preferred terms 'Neoplasm Progression', 'Malignant Neoplasm Progression' and 'Disease Progression' not related to the study drug are excluded
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Grades are based on NCI CTCAE version 4.03 and MedDRA version is 24.1
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Table 18 Participants With Adverse Events by AEOSI Category and Preferred Term (Incidence > 0%) - Participants: MSI-H with Small Intestine Cancer (ASaT Population)

	Pembrolizumab 200 mg Q3W	
	n	(%)
Participants in population	27	
with one or more adverse events		
with no adverse events		
Colitis		
Colitis		
Hepatitis		
Hepatitis		
Hyperthyroidism		
Hyperthyroidism		
Hypothyroidism		
Hypothyroidism		
Pancreatitis		
Pancreatitis		
Pneumonitis		
Interstitial lung disease		
Pneumonitis		

Every participant is counted a single time for each applicable row and column.
A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
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Table 19 KEYNOTE-061 (gastric) – efficacy outcomes in pembrolizumab and paclitaxel groups (MSI-H and non-MSI-H subgroups)

	Pembrolizumab			Paclitaxel		
	MSI-H subgroup, n=15	**Non-MSI-H* subgroup, n=281**	**All patients, n=296**	**MSI-H subgroup, n=12**	**Non-MSI-H* subgroup, n=284**	**All patients, n=296**
ORR, % (95% CI)	46.7 (21.3 – 73.4)	9.3 (6.2 – 13.3)	11.1 (7.8 – 15.3)	16.7 (2.1 – 48.4)	12.3 (8.7 – 16.7)	12.5 (9.0- 16.8)
DOR, median (range), months	NR (5.5. – 26.0)	Not available	18.0 (1.4 – 26.0)	NR (2.2 – 12.2)	Not available	5.5 (1.3 – 17.7)
Median PFS (95% CI), months	17.8 (2.7 – NR)	1.5 (1.4 – 1.6)	1.5 (1.4 – 1.6)	3.5 (2.0 – 9.8)	4.1 (3.2 – 4.2)	4.1 (3.2-4.2)
Median OS (95% CI), months	NR (5.6 – NR)	6.5 (5.0 – 8.6)	6.7 (5.4 – 8.9)	8.1 (2.0 – 16.7)	8.3 (7.6-8.9)	8.3 (7.7- 8.8)
OS rate, % (95% CI), 12 months	73 (44-89)	32.0 (26.7 – 37.5)	34 (29 – 39)	25 (6-50)	28.3 (23.3- 33.6)	28 (23-33)
OS rate, % (95% CI), 24 months	59 (31 – 79)	Not available	18 (13 – 23)	Not available	Not available	9 (6-13)

*non-MSI-H status includes patients not evaluable for MSI-H
Abbreviations: DOR, duration of response; MSI-H, microsatellite high; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival
Notes: Median (range) follow-up: 7.9 (0.2-27.7) months
Source: Chao et al. 2021 (11)

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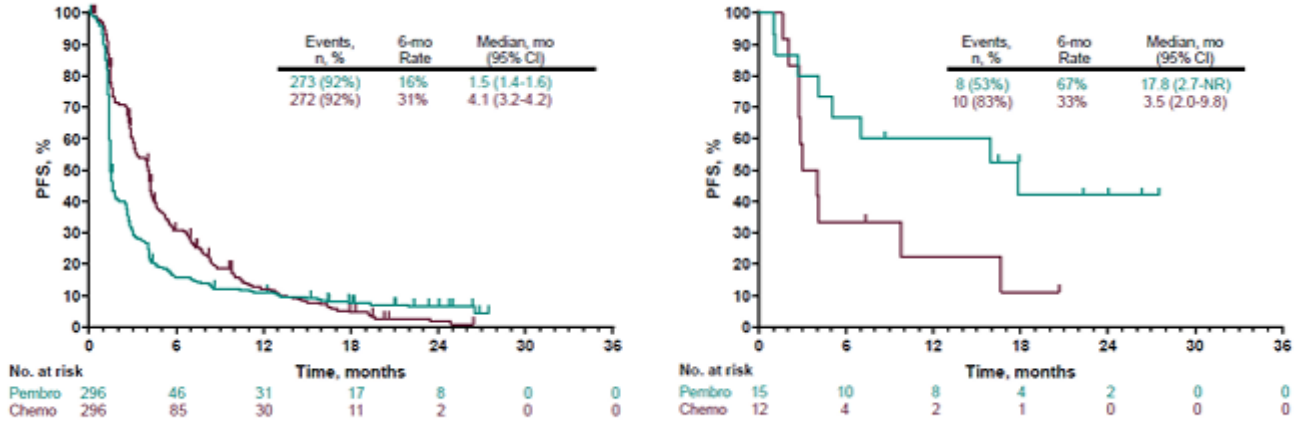
Figure 1 Kaplan-Meier estimates of PFS in patients with advanced gastric cancer (KEYNOTE-061); all patients (left), patients with MSI-H tumours (right)



Source: Chao et al. 2021 (11)

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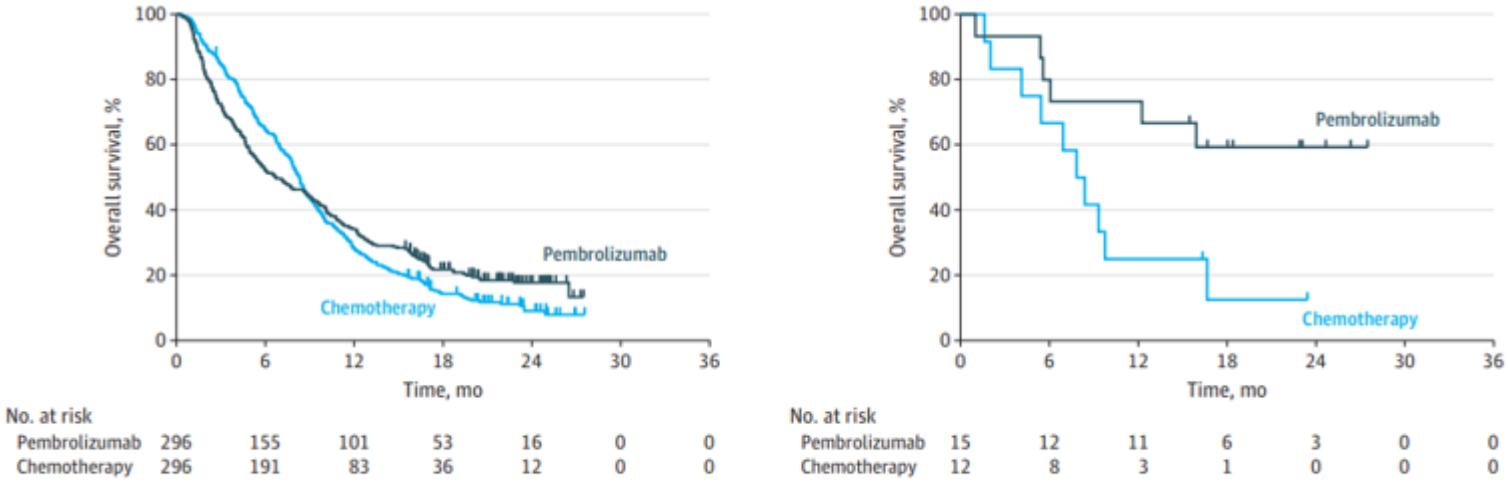
Figure 2 Kaplan-Meier estimates of OS in patients with advanced gastric cancer (KEYNOTE-061); all patients (left), patients with MSI-H tumours (right)



Source: Chao et al. 2021 (11)

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Table 20 Baseline characteristics of patients with advanced gastric cancer (KEYNOTE-061)

	KEYNOTE-061, MSI-H, n=27		KEYNOTE-061, non-MSI-H or MSI-H non-evaluable, n=565	
	Pembrolizumab, n=15	Paclitaxel, n=12	Pembrolizumab, n = 281	Paclitaxel, n=284
Age, median (range), years	67 (36-76)	63 (43-75)	62 (27-87)	60.0 (20-86)
Male	7 (46.7)	8 (66.7)	195 (69)	200 (70)
Australia/Europe/ North America	10 (66.7)	7 (58.3)	180 (64)	180 (63)
Asia	4 (26.7)	3 (25.0)	84 (30)	86 (30)
Rest of World	1 (6.7)	2 (16.7)	17 (6)	18 (6)
ECOG PS 0	5 (33.3)	4 (33.3)	122 (43)	133 (47)
ECOG PS 1	10 (66.7)	8 (66.7)	159 (57)	150 (53)
Metastatic disease	14 (93.3)	11 (91.7)	278 (99)	283 (100)
Stomach	11 (73.3)	10 (83.3)	196 (70)	190 (67)
Gastroesophageal junction adenocarcinoma	4 (26.7)	2 (16.7)	85 (30)	94 (33)
Diffuse subtype adenocarcinoma	4 (26.7)	2 (16.7)	81 (29)	63 (22)

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Intestinal subtype adenocarcinoma	0	4 (33.3)	44 (16)	70 (25)
Mixed/Unknown subtype	11 (73.3)	6 (50.0)	157 (55)	151 (53)
0 prior therapies	0	0	0	0
1 prior therapy	15 (100)	12 (100)	281 (100)	284 (100)
≥2 prior therapies	0	0	0	0
PD-L1 CPS ≥1	13 (86.7)	11 (91.7)	183 (65)	188 (66)

Abbreviations: CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability high; PD-L1, programmed cell death 1 ligand 1.
Source: Chao et al. 2021 (11)

Table 21 ZEBRA study (small intestine cancer) - efficacy outcomes in MSI-H and non-MSI-H subgroups treated with pembrolizumab

	Pembrolizumab	
	Non-MSI-H subgroup, n=32	**MSI-H subgroup, n=4**
ORR, %	8% (2-20) (all patients)	50%
Median DOR (range), months	17.5 (3.0 – 32.1)	28.5 (26.5 – 30.5)
Number of PFS events/Total	31/32	2/4
Median PFS (95% CI), months	2.8 (2.7 – 4.2)	NE (2.5, NE)
Number of OS events/Total	28/32	2/4

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Median OS (95% CI), months	6.6 (4.8 – 12.0)	NE (2.5, NE)

Notes: Within the allcomers study population, three confirmed PRs were observed, of which 2/4 in MSI-H subgroup and one/32 (3%) in patients with MSS/MSI-L status confirmed
Source: Pedersen et al. 2021 (12)

Table 22 KEYNOTE-158 (biliary cancer) - efficacy outcomes in MSI-H and non-MSI-H cohorts treated with pembrolizumab

	Pembrolizumab	
	MSI-H population (cohort K)[a], n=22	**Non-MSI-H population[b], n=104**
ORR, % (95% CI)	40.9 (20.7, 63.6)	5.8 (2.1- 12.1)
DOR, median (range), months	30.6 (6.2 - 46.0+)	NR (6.2-26.6+)
Median PFS (95% CI), months	4.2 (2.1, 24.9)	2.0 (1.9-2.1);
PFS rate, %, 12 months	36.4	5.2
Median OS (95% CI), months	19.4 (6.5, 44.8)	7.4 (5.5-9.6);
OS rate, %, 12 months	63.6	32.7

[a] Data cut-off: 15-OCT-2021; median (range) follow-up: 19.4 (1.1, 60.8) months
[b] Data cut-off: 6-DEC-2018; median (range) follow-up: 7.5 (0.6-34.3) months
Notes: non-MSI-H population includes 99 (95.2) patients with negative MSI status and 5 (4.8) patients with missing MSI status (insufficient tissue for MSI testing, poor quality DNA, testing failure and lack of appropriate consent for necessary genetic testing)
Source: Piha-Paul et al. 2020 (13).

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Table 23 Baseline characteristics for MSI-H and non-MSI-H biliary cancer cohorts treated with pembrolizumab (KEYNOTE-158)

	MSI-H population (cohort K), n=22		Non-MSI-H population, n=104	
	n	%	n	%
Participants in population	22		104	
Sex				
Male	16	73%	51	49%
Female	6	27%	53	51%
Age (Years)				
>= 65	9	41%	44	42.3%
Median	60.5		63	
Range	40 to 77		34 to 81	
Race				
Asian	2	9%	37	35.6%
Black Or African American			0	
White	20	91%	67	64.4%
Missing			0	
ECOG				
[0] Normal Activity	10	46%	42	40.4%
[1] Symptoms, but ambulatory	12	55%	62	59.6%
Number of Prior Lines of Therapy				
0	2	9%	1	1.07%
1	11	50%	42	40.4%
2	6	27%	37	35.6%
3	1	5%	14	13.5%
4	2	9%	8	7.7%
5 or more			2	1.9%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability high

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Notes: non-MSI-H population includes 99 (95.2) patients with negative MSI status and 5 (4.8) patients with missing MSI status (insufficient tissue for MSI testing, poor quality DNA, testing failure and lack of appropriate consent for necessary genetic testing)
Source: Piha-Paul et al. 2020 (13).

Table 24 KEYNOTE-775 (endometrial cancer) - efficacy outcomes in dMMR and pMMR subgroups treated with TPC

	TPC (paclitaxel or doxorubicin)		
	dMMR subgroup, n=65	**pMMR subgroup, n=351**	**All patients, n=416**
ORR, % (95% CI)	12 (5 – 23)	15.1 (11.5 -19.3)	14.7 (11.4 –18.4)
DOR, median (range), mo	4.1 (1.9 – 15.6)	5.7 (0.0 – 24.2)	5.7 (0.0 – 24.2)
Median PFS (95% CI), mo	3.7 (3.1 – 4.4)	3.8 (3.6 – 5.0)	3.8 (3.6 – 4.2)
PFS rate, % (95% CI), 6 months	24.8 (14.3 – 36.8)	36.2 (30.5 – 41.9)	34.3 (29.2 – 39.4)
PFS rate, % (95% CI), 12 months	12.9	13.1 (8.9 – 18.3)	13.2 (9.3 – 17.8)
Median OS (95% CI), mo	8.6 (5.5 – 12.9)	12.0 (10.8 – 13.3)	11.4 (10.5 – 12.9)
OS rate, % (95% CI), 12 months	39.1 (26.7 – 51.3)	49.5 (43.8 – 55.0)	47.9 (42.7 – 53.0)
OS rate, % (95% CI), 24 months	Not available	21.5 (13.9- 30.1)	21.4 (14.2 – 29.6)

Abbreviations: dMMR, mismatch repair deficient; pMMR, mismatch repair proficient; TPC, treatment physician's choice
Source: Makker et al. 2022 (14); EPAR EMEA/H/C/003820/II/0105 (17)

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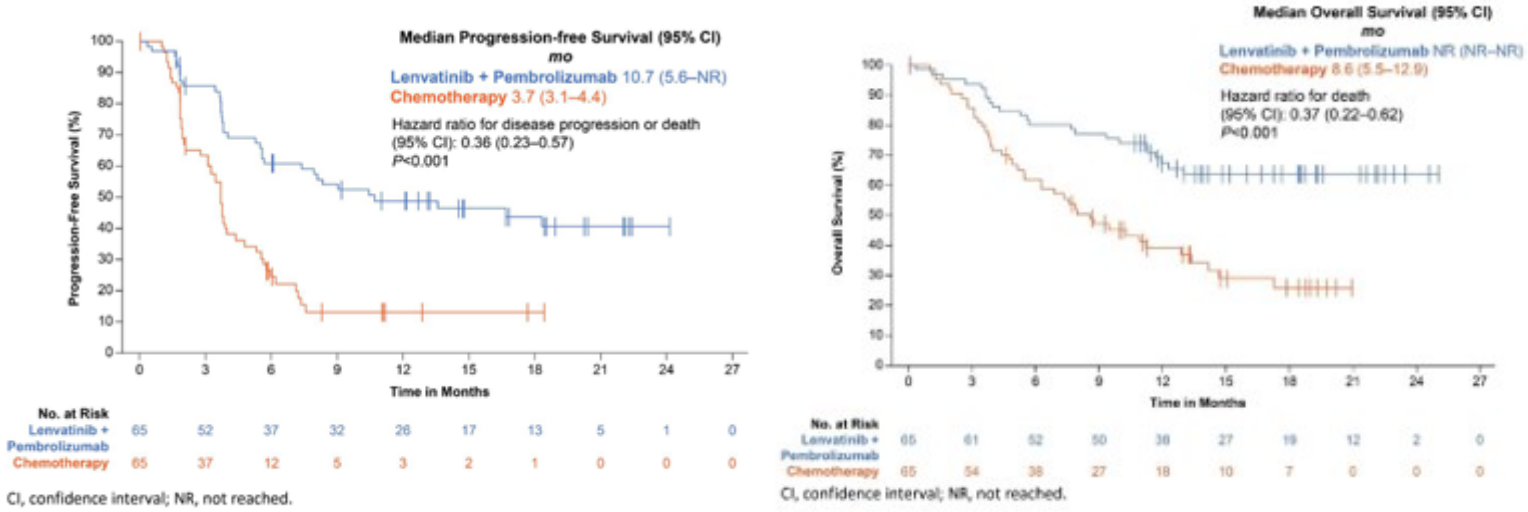
Figure 3 KEYNOTE-775 (endometrial cancer) – KM estimates of PFS (left) and OS (right) in dMMR patients treated with TPC (red curve)



Source: Makker et al. 2022 (14)

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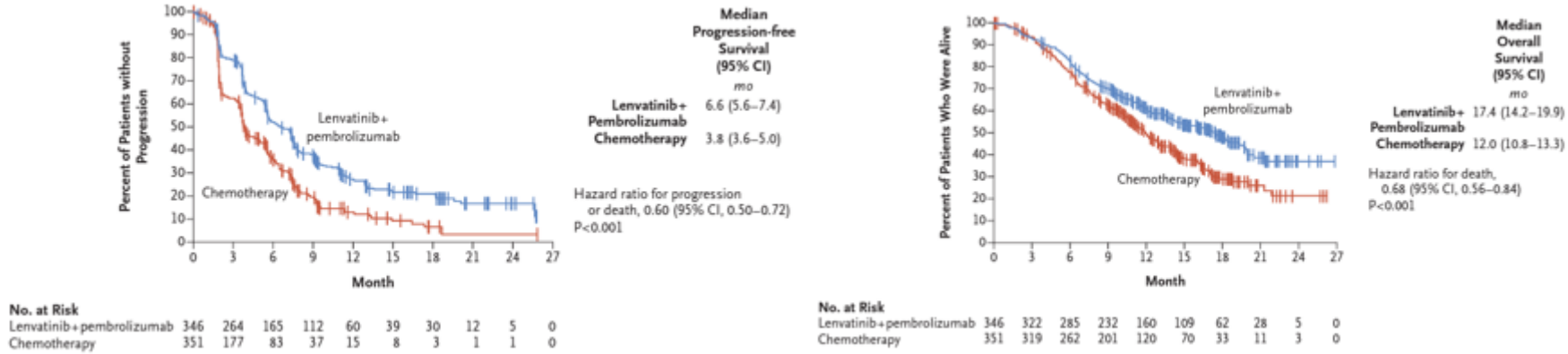
Figure 4 KEYNOTE-775 (endometrial cancer) – KM estimates of PFS (left) and OS (right) in pMMR patients treated with TPC (red curve)



Source: Makker et al. 2022 (14)

Table 25 Baseline characteristics of patients with endometrial cancer treated with TPC (KEYNOTE-775)

	TPC (paclitaxel or doxorubicin)	
	dMMR subgroup, n=65	**pMMR subgroup, n=351**
Median age (range), years	63.0	66 (35-86)
Race*, n (%)		
White	35 (53.8)	211 (60.1)
Asian	12 (18.5)	80 (22.8)
Black	5(7.7)	9 (2.6)
ECOG status, n (%)		
0	34 (52.3)	207 (59.0)

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1	31 (47.7)	144 (41.0)

Abbreviations: dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; pMMR, mismatch repair proficient; TPC, treatment physician's choice
Notes: Data on race were missing for 10.3% patients in the chemotherapy group (pMMR subgroup). Other races or ethnic groups (reported by 4.3% in the pMMR chemotherapy group) included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiple.
Source: Makker et al. 2022 (14)

Table 26 Efficacy outcomes in dMMR subgroup (KEYNOTE-775) vs unselected population (McMeekin 2015) treated with TPC (endometrial cancer)

	TPC (paclitaxel or doxorubicin)		
	dMMR subgroup (KN-775), n=65	**Unselected population (McMeekin 2015), n=248**	**Overall population (KN-775), n=416**
ORR, %(95% CI)	12 (5 – 23)	15.7 (11.2, 21.1)	14.7 (11.4 – 18.4)
DOR, median (range), mo	4.1 (1.9 – 15.6)	Not available	5.7 (0.0 – 24.2)
Median PFS (95% CI), mo	3.7 (3.1 – 4.4)	4.0 (2.7, 4.3);	3.8 (3.6 – 4.2)
Median OS (95% CI), mo	8.6 (5.5 – 12.9)	12.3 (10.7–15.4)	11.4 (10.5 – 12.9)
OS rate, % (95% CI), 12 months	39.1 (26.7 – 51.3)	53	47.9 (42.7 – 53.0)
OS rate, % (95% CI), 24 months	Not available	30	21.4 (14.2 – 29.6)

Source: McMeekin et al. 2015 (15) and Makker et al. 2022 (14)

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036] – Additional scenario analyses

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Center+ (UMC+)

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Date completed 22/03/2023

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number STA 13/57/86.

Declared competing interests of the authors None.

Acknowledgements

We gratefully acknowledge the expert advice input from Veerle Coupe, Department of Epidemiology and Data Science, Amsterdam Public Health, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, the Netherlands.

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This report should be referenced as follows:

Perry M, Witlox W, Grimm S, Sugden B, Abu-Zarah T, Otten T, Patel M, Noake C, Armstrong N, Joore M, Wolff R. Pembrolizumab for previously treated solid tumours with high microsatellite instability or mismatch repair deficiency [ID4036]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2023.

Contributions of authors

Mark Perry and Mubarak Patel acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Sabine Grimm, Bradley Sugden, Teebah Abu-Zarah, Thomas Otten, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance. Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report.

Deterministic/probabilistic company's and EAG base-case – overall indication

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]	iNHB[2]
Company's and EAG's deterministic base-case							
SoC	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Double subsequent treatment costs for pembrolizumab)							
SoC	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Subsequent treatment costs based on proportional difference in survival benefit between arms)							
SoC	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (1.2 severity modifier for colorectal and endometrial cancer, 1.7 severity modifier for gastric, small intestine and biliary cancer)							
SoC	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

[1]iNHB for willingness-to-pay of £30,000 per QALY

[2]iNHB for willingness-to-pay of £20,000 per QALY

Fully incremental analyses of company's and EAG base-case – colorectal cancer

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]	iNHB[2]
Company's and EAG's updated deterministic base-case							
TAS-102	[redacted]	[redacted]	-	-	-	-	-
Pooled FOLFOX/FOLFIRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Double subsequent treatment costs for pembrolizumab)							
TAS-102	[redacted]	[redacted]	-	-	-	-	-
Pooled FOLFOX/FOLFIRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Subsequent treatment costs based on proportional difference in survival benefit between arms)							
TAS-102	[redacted]	[redacted]	-	-	-	-	-
Pooled FOLFOX/FOLFIRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*****
Deterministic Scenario analysis (1.2 severity modifier for colorectal and endometrial cancer, 1.7 severity modifier for gastric, small intestine and biliary cancer)							
TAS-102	[redacted]	[redacted]	-	-	-	-	-
Pooled FOLFOX/FOLFIRI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom
[1]iNHB for willingness-to-pay of £30,000 per QALY
[2]iNHB for willingness-to-pay of £20,000 per QALY

Fully incremental analyses of company's and EAG base-case – endometrial cancer

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]	iNHB[2]
Company's and EAG's updated deterministic base-case							
Doxorubicin	[redacted]	[redacted]	-	-	-	-	-
Paclitaxel	[redacted]	[redacted]	-	-	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Double subsequent treatment costs for pembrolizumab)							
Doxorubicin	[redacted]	[redacted]	-	-	-	-	-
Paclitaxel	[redacted]	[redacted]	-	-	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Subsequent treatment costs based on proportional difference in survival benefit between arms)							
Doxorubicin	[redacted]	****	-	-	-	-	-
Paclitaxel	[redacted]	****	-	-	[redacted]	-	-
Pembrolizumab	[redacted]	****	[redacted]	[redacted]	[redacted]	[redacted]	****
Deterministic Scenario analysis (1.2 severity modifier for colorectal and endometrial cancer, 1.7 severity modifier for gastric, small intestine and biliary cancer)							
Doxorubicin	[redacted]	[redacted]	-	-	-	-	-
Paclitaxel	[redacted]	[redacted]	-	-	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom
[1]iNHB for willingness-to-pay of £30,000 per QALY
[2]iNHB for willingness-to-pay of £20,000 per QALY

Fully incremental analyses of company's and EAG base-case – gastric cancer

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]	iNHB[2]
Company's and EAG's updated deterministic base-case							
FOLFIRI	[redacted]	[redacted]	-	-	-	-	-
Paclitaxel	[redacted]	[redacted]	-	-	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Double subsequent treatment costs for pembrolizumab)							
FOLFIRI	[redacted]	[redacted]	-	-	-	-	-
Paclitaxel	[redacted]	[redacted]	-	-	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*****
Deterministic Scenario analysis (Subsequent treatment costs based on proportional difference in survival benefit between arms)							
FOLFIRI	[redacted]	[redacted]	-	-	-	-	-
Paclitaxel	[redacted]	[redacted]	-	-	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*****
Deterministic Scenario analysis (1.2 severity modifier for colorectal and endometrial cancer, 1.7 severity modifier for gastric, small intestine and biliary cancer)							

FOLFIRI	[redacted]		-	-	-	-	-
Paclitaxel	[redacted]		-	-	[redacted]	-	-
Pembrolizumab	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom
[1]iNHB for willingness-to-pay of £30,000 per QALY
[2]iNHB for willingness-to-pay of £20,000 per QALY

Fully incremental analyses of company's and EAG base-case – small intestine cancer

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]	iNHB[2]
Company's and EAG's updated deterministic base-case							
Nab-paclitaxel	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Double subsequent treatment costs for pembrolizumab)							
Nab-paclitaxel	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Subsequent treatment costs based on proportional difference in survival benefit between arms)							
Nab-paclitaxel	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (1.2 severity modifier for colorectal and endometrial cancer, 1.7 severity modifier for gastric, small intestine and biliary cancer)							
Nab-paclitaxel	[redacted]	[redacted]	-	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom
[1]iNHB for willingness-to-pay of £30,000 per QALY
[2]iNHB for willingness-to-pay of £20,000 per QALY

Fully incremental analyses of company's and EAG base-case – cholangiocarcinoma

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB[1]	iNHB[2]
Company's and EAG's updated deterministic base-case							
mFOLFIRI	[redacted]		-	-	-	-	-
mFOLFOX	[redacted]		-	-	[redacted]	-	-
Pembrolizumab	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Double subsequent treatment costs for pembrolizumab)							
mFOLFIRI	[redacted]		-	-	-	-	-
mFOLFOX	[redacted]		-	-	[redacted]	-	-
Pembrolizumab	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (Subsequent treatment costs based on proportional difference in survival benefit between arms)							
mFOLFIRI	[redacted]		-	-	-	-	-
mFOLFOX	[redacted]		-	-	[redacted]	-	-
Pembrolizumab	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic Scenario analysis (1.2 severity modifier for colorectal and endometrial cancer, 1.7 severity modifier for gastric, small intestine and biliary cancer)							

mFOLFIRI	[redacted]	[redacted]	-	-	-	-	-
mFOLFOX	[redacted]	[redacted]	-	-	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; QALY = quality-adjusted life-year; SoC = standard of care; UK = United Kingdom

[1]iNHB for willingness-to-pay of £30,000 per QALY

[2]iNHB for willingness-to-pay of £20,000 per QALY

EAG's fully incremental results without QALY weights

Tumour site	Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Colorectal	TAS-102	£24,407	[redacted]	-	-	-
	Pooled FOLFOX/FOLFIRI	£27,511	[redacted]	[redacted]	[redacted]	£11,014
	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£16,754
Endometrial	Doxorubicin	£18,101	[redacted]	-	-	-
	Paclitaxel	£22,803	[redacted]	[redacted]	[redacted]	Dominated
	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£21,497
Gastric	FOLFIRI	£24,567	[redacted]	-	-	-
	Paclitaxel	£29,623	[redacted]	[redacted]	[redacted]	Extendedly dominated
	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£32,865
Small intestine	Nab-paclitaxel	£34,793	[redacted]	-	-	-
	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,928
Biliary (cholangiocarcinoma)	mFOLFIRI	£13,300	[redacted]	-	-	-
	mFOLFOX	£17,109	[redacted]	[redacted]	[redacted]	Extendedly dominated
	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,061
Overall indication	**SoC**	**£25,634**	[redacted]	**-**	**-**	**-**
	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	**£22,655**