Single Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

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 Bristol-Myers Squibb :**
   a. Full submission
   b. Addendum to submission
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response
   b. Addendum

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Bowel Cancer UK

4. **Expert personal perspectives** from:
   a. Jenny Seligmann, Professor of Gastrointestinal Oncology and Honorary Consultant Medical Oncologist – clinical expert, nominated by BMS (company)
   b. Richard Wilson – clinical expert

5. **External Assessment Report** prepared by PenTAG

6. **External Assessment Report – factual accuracy check**

7. **Comparison of Updated Kaplan Meier Data to Model Predictions**
   a. Summary of CheckMate 8HW Interim Analysis 1b November 2024
   b. Comparison of Updated Kaplan Meier Data to Model Predictions

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

Nivolumab plus ipilimumab for the treatment of adults and adolescents with untreated metastatic colorectal cancer with high microsatellite instability or deficient mismatch repair (ID1136)

Document B

Company evidence submission

June 2024

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		Yes	**26th June 2024**

Contents

Tables and figures

Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
AACR	American Association for Cancer Research
AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
ASCRS	American Society of Colon and Rectal Surgeons
AST	Aspartate aminotransferase
BICR	Blinded independent central review
BOR	Best overall response
BSC	Best supportive care
C19	Coronavirus-19
CADTH	Canadian Agency for Drugs and Technologies in Medicine
CAPOX	Capecitabine + oxaliplatin
CD28	Cluster of differentiation 28
CD80	Cluster of differentiation 80
CD86	Cluster of differentiation 86
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Controlled Register of Trials
CI	Confidence interval
CLCr	Clearance of creatinine
CM142	CheckMate 142
CM8HW	CheckMate 8HW
CP3A4	Cytochrome P450 3A4
CR	Complete response
CRC	Colorectal cancer
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CRR	Complete response rate
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTLA-4	Cytotoxic T-lymphocyte antigen-4
D	Death state
DCR	Disease control rate

DG27	Diagnostics Guidance 27
DIC	Deviance information criterion
dMMR	DNA mismatch repair deficient
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
EAG	External assessment group
ECOG PS	Eastern Cooperative Oncology Group Performance Score
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
Embase	Excerpta Medica Database
eMIT	Electronic market information tool
ERG	Evidence review group
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Core Questionnaire
EORTC QLQ-CR29	European Organisation for the Research and Treatment of Cancer 29-item Quality of Life Questionnaire
EQ-5D-(3L)	EuroQol 5-dimensional questionnaire (3 levels)
ESCP	European Society of Coloproctology
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FIT	Faecal immunochemical tests
FOLFIRI	Folinic acid + fluorouracil + irinotecan
FOLFOX	Folinic acid + fluorouracil + oxaliplatin
FOLFOXIRI	Folinic acid + fluorouracil + oxaliplatin + irinotecan
FP	Fractional polynomial
gFOBT	Guaiac-based faecal occult blood test
GI	Gastrointestinal
GX	Grade undetermined
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
$IgG1_{\kappa}$	Immunoglobulin G1 light chain
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IMAE	Immune-mediated adverse event
INR	International Normalised Ratio
IO	Immunotherapy

IPI	Ipilimumab
IRP	International recognition procedure
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KN-177	KEYNOTE-177
LS	Least squares
LY	Life-year
MCID	Minimum clinically important difference
mCRC	Metastatic colorectal cancer
MAIC	Matching adjusted indirect comparison
MEDLINE	Medical Literature Analysis and Retrieval System Online
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	Modified FOLFOX
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSI-L	Microsatellite instability low
MSS	Microsatellite stable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab
NMA	Network meta-analysis
OD	Once daily
OESI	Other events of special interest
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PAN	Panitumumab
PAS	Patient access scheme
PCR	Polymerase chain reaction
PD	Progressed disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PD-L2	Programmed death ligand-2
PEMBRO	Pembrolizumab

PF	Progression-free
PFS	Progression-free survival
PHA	Proportional hazards assumption
PICOS	Population, intervention, comparison, outcomes, study design
PK	Pharmacokinetic
pMMR	DNA mismatch repair proficient
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PT/INR	Prothrombin time test/International Normalised Ratio
PT	Preferred term
PTT	Partial thromboplastin time
RFS	Relapse-free survival
QALY	Quality-adjusted life-year
QoL	Quality of life
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
SAE	Serious adverse events
SIRT	Selective internal radiation therapy
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SOC	System organ class
TA	Technology assessment
TEM	Treatment effect modifiers
TMB	Tumour mutational burden
TNM	Tumour/node/metastasis
TRAE	Treatment-related adverse events
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
TTR	Time to response
UGT1A1	UDP-glucuronosyltransferase 1-1
UI	Utility index

UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
VBA	Visual basic applications
WBC	White blood cell
WOCBP	Women of childbearing potential
WTP	Willingness-to-pay

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

B.1.1 Decision problem

This submission covers the full anticipated marketing authorisation for nivolumab plus ipilimumab (NIVO + IPI). We anticipate that NIVO + IPI will be indicated for the first-line (1L) treatment of adult and adolescent patients, 12 years and older, with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC). The decision problem addressed is consistent with the final NICE scope and the NICE reference case as outlined in Table 1.

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	People aged 12 years and older with previously untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatched repair deficiency	As per NICE scope	N/A
Intervention	Nivolumab + ipilimumab (NIVO + IPI)	As per NICE scope	N/A
Comparator(s)	For all people: • Pembrolizumab (PEMBRO) • Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Capecitabine plus oxaliplatin (CAPOX) • Capecitabine For people with RAS mutant mCRC: • Folinic acid plus fluorouracil plus oxaliplatin plus irinotecan (FOLFOXIRI) For people with RAS wild type mCRC:	As per NICE scope	• FOLFOX, FOLFIRI and CAPOX are similarly effective, as are cetuximab and panitumumab, as noted in TA709.[1] Therefore, where direct comparisons are missing, equal effectiveness may be assumed across these groups. An ITC scenario assesses the comparison of NIVO + IPI versus panitumumab with FOLFOX. • In addition, according to expert opinion, cetuximab- and panitumumab-containing

	• Panitumumab in combination with FOLFOX or FOLFIRI For people with EGFR expressing, RAS wild-type mCRC: • Cetuximab in combination with FOLFOX or FOLFIRI		regimens are only prescribed 5–7.5% of the time in dMMR/MSI-H mCRC • Capecitabine monotherapy is only used in elderly and frail patients with an ECOG PS of > 1, meaning that it is not relevant for the CM8HW population[1,2]
Outcomes	• OS • PFS • Response rates • AEs of treatment • QoL	As per NICE scope	N/A
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	As per NICE scope	N/A

	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability and cost of biosimilar and generic products should be taken into account. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.		
Subgroups to be considered	If evidence allows, subgroups based on RAS mutation status will be considered.	• BRAF/KRAS/NRAS mutation status (efficacy data reported) • Patients treated without bevacizumab (efficacy data reported)	• In the CM8HW subgroup analysis, the HR for progression in the KRAS-mutant subgroup (n=45) was similar to the HR (95% CI) for the whole centrally-confirmed population (0.24 [0.09, 0.63] vs. 0.20 [0.14, 0.31]). KRAS mutation appears to have no significant impact on the comparative efficacy of NIVO + IPI. • Subgroup analysis for bevacizumab was conducted because it is no longer recommended by NICE in this indication

Special considerations including issues related to equity or equality	N/A	No equality issues have been identified or are anticipated	N/A

Abbreviations: AE, adverse event; CM8HW, CheckMate 8HW; dMMR, DNA mismatch repair deficiency; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IPI, ipilimumab; MSI-H, microsatellite instability high; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NIVO, nivolumab; OS, overall survival; PEMBRO, pembrolizumab; PFS, progression-free survival; QALY, quality adjusted life-year; QoL, quality of life

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in this submission are summarised in Table 2 and detailed in the following subsections. Additionally, the Summary of Product Characteristics for nivolumab (Opdivo®) and ipilimumab (Yervoy®) is presented in Appendix C.

Table 2. Technology being considered

UK approved name and brand name	Nivolumab (Opdivo®) Ipilimumab (Yervoy®)
Mechanism of action	NIVO is a human IgG4 monoclonal antibody, which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2.[3] IPI is a human IgG1κ monoclonal antibody. It is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway.[4] In human T-cells, dual blockade of PD-1 and CTLA-4 resulted in synergistic activity.[5]
Marketing authorisation/ CE mark status	[redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	It is anticipated that NIVO + IPI will be indicated for the 1L treatment of adult and adolescent patients, 12 years and older, with unresectable or metastatic dMMR/MSI-H CRC. NIVO + IPI also holds marketing authorisation for: • Advanced (unresectable or metastatic) melanoma in adults and adolescents, aged 12 years and older • Metastatic non-small cell lung cancer • Unresectable malignant pleural mesothelioma

	• First line treatment of adult patients with immediate/poor risk advanced renal cell carcinoma • Unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1% • Previously-treated dMMR/MSI-H mCRC Though these are not the subject of this submission.
Method of administration and dosage	**Adult patients and adolescent patients 12 years and older and weighing 40 kg or more:** [redacted] **Adolescent patients 12 years and older and weighing less than 40 kg:** [redacted]
Additional tests or investigations	No additional tests are required. Patients eligible to receive NIVO + IPI have mismatch dMMR/MSI-H mCRC. Current NICE guidance recommends that all people with colorectal cancer should be offered testing when first diagnosed, using immunohistochemistry to detect DNA mismatch repair proteins or PCR to detect microsatellite instability, based on economic evaluations conducted as part of Diagnostics Guidance 27 [DG27]. Therefore, all patients will already be offered testing to identify dMMR/MSI-H status. It should be noted that this early testing will also inform other treatment choices.
List price and average cost of a course of treatment	NIVO is £2633 per 240mg vial. IPI is £3,750 per 10-ml (50-mg) vial.
Patient access scheme (if applicable)	Patient access schemes are in place for both NIVO and IPI

Abbreviations: 1L, first-line; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte antigen-4; dMMR, DNA mismatch repair deficiency; IgG4, human immunoglobulin G4; IRP, International Recognition Procedure; MHRA, Medicines and Healthcare products RMSI-H, microsatellite instability high; PD-1, programmed death 1; PD-L1, programmed death ligand 1

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

B.1.3.1 Disease Overview

B.1.3.1.1 Disease background

CRC is a malignant tumour that arises from the lining of the large intestines (colon and rectum). CRC is generally considered advanced when the primary cancer has spread to another part of the body (metastatic) or in some cases has spread into tissues around the bowel or nearby lymph nodes (locally advanced).[6] In some rare instances, advanced CRC may also refer to tumours that have grown into or through the outer lining of the bowel, and are therefore considered unresectable via surgery.

Metastatic CRC (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes.[7] The most common sites of metastasis are the liver, the lungs and the peritoneum, however, the cancer may also spread to other sites, such as the bones or the brain.[8] Hepatic metastases are detected in more than 25% of CRC patients within five years of diagnosis of the primary tumour, making up 60–70% of all metastases diagnosed.[9-11]

Metastases are often synchronous in CRC; that is, they are often present at diagnosis of the primary tumour. Recent UK observational studies have reported that ≥ 70% of prevalent mCRC cases are diagnosed when the cancer is already metastatic,[12-14] and European observational studies have found that most hepatic metastases (around 60%) are synchronous.[9,15] Therefore, mCRC is often diagnosed late in the disease course.

CRC represents the second most common cause of cancer death in the UK, accounting for 10% of total cancer mortality in 2020.[16]

B.1.3.1.1.1 The dMMR/MSI-H subtype

Around 4–5% of mCRC tumours are classed as dMMR.[17,18] Mismatch repair status may be assessed via an immunohistochemistry (IHC) panel, and is commonly associated with methylation of the MLH1 gene promoter, although there are other

genetic types. Other genes associated with dMMR include MSH2, MSH6 and PMS2.[19-23]

dMMR is a distinct molecular subtype of CRC, characterised by an inability to repair certain classes of spontaneous mutations within repetitive DNA sequences or microsatellites, generally resulting in MSI-H.[24-26] Microsatellite instability (MSI) itself may be assessed by examining repeat sizes of microsatellite markers, using next-generation sequencing. While most dMMR tumours display MSI-H, this is not always the case and results may be discordant.[23] However, these tests are highly correlated and the discordance rate is low (1.6%–3.4%),[27-29] meaning that generally it is not considered necessary to perform both tests.[30]

Tumours with dMMR/MSI-H are biologically distinct from tumours that are microsatellite stable (MSS) or have low microsatellite instability (MSI-L). MSI-H tumours tend to be poorly-differentiated and right-sided.[17,31-33] In a Scandinavian real-world cohort (n = 583), 85% of MSI-H tumours were right-sided, compared with 32% of MSS tumours.[33] Additionally, an analysis of 101,259 adrenal carcinomas identified from the US National Cancer Database found that 25.3–25.5% of right-sided CRC tumours were dMMR/MSI-H, compared with 7.6–18.3% of left-sided tumours.[31]

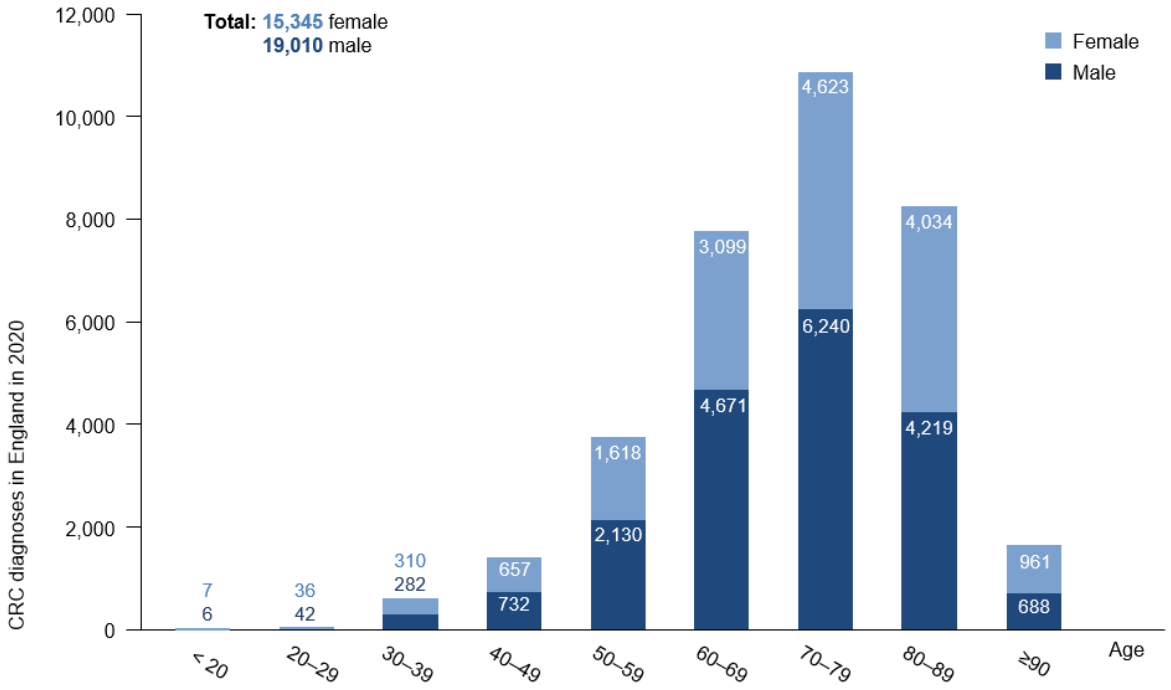
There are also differences in the tumour microenvironment, with MSI-H tumours demonstrating significantly upregulated expression of immune checkpoints such as programmed death ligand 1 (PD-L1) and cytotoxic lymphocyte antigen-4 (CTLA-4).[34] Hence, this subtype may be more susceptible to immune checkpoint blockade.[18,24,35,36] In addition, tumour mutation burden TMB itself may be a biomarker for the effectiveness of immune checkpoint inhibitor (ICI) therapy in tumours with dMMR/MSI-H.[37-39]

B.1.3.1.1 Epidemiology

CRC is the third most common cancer diagnosed worldwide,[40] and the fourth most common cancer in the UK.[16] In 2020, 34,405 new cases of CRC were diagnosed in England. Incidence rises sharply with age, and is highest in people aged 70–79, with more than 90% of cases diagnosed in those 50 and older.[16] However, the incidence

of CRC in the population aged under 50 is increasing,[41] with those under 50 more likely to be diagnosed at a later stage and with less differentiated CRC.[42] 55.3% of cases were diagnosed in males (Figure 1). There were 14,033 deaths due to CRC in 2020.[16]

Figure 1. Cases of CRC diagnosed in England in 2020, stratified by age



Abbreviations: CRC, colorectal cancer

A considerable proportion of newly-diagnosed CRC in England is diagnosed as mCRC (stage IV), and survival in this group is poor. Over the period 2016–2020, 170,859 cases of CRC were newly diagnosed in England, with 38,729 (22.7%) of these being diagnosed as mCRC. For all stages at diagnosis, 1-year overall survival (OS) was 77.2%, 2-year OS was 68.1%, and 5-year OS was 60.0%. In the group diagnosed at stage IV, survival rates were much poorer; 1-year OS was 45.0%, 2-year OS was 28.4% and 5-year OS was 18.8%.[43] Therefore, there is a significant unmet need for new and effective treatments in this population due to their poor survival.

B.1.3.1.2 Diagnosis

CRC may be suspected based on symptoms, physical examination, and the results of faecal immunochemical tests (FIT) and blood tests.[44] General symptoms associated with the presence of a primary tumour may include rectal bleeding,

abdominal pain, diarrhoea/constipation, abdominal mass which may be felt during a physical examination, weight loss, tiredness and breathlessness.

In addition, the bowel may have become obstructed, leading to symptoms including cramping, bloating, constipation and vomiting.[45] Diagnosis of suspected CRC is confirmed by biopsy.[44]

Once CRC is confirmed, disease stage and metastatic status is identified by radiological imaging and histology of the primary tumour and metastases.[44] If CRC is not metastatic at diagnosis, patients will be followed for three years following curative treatment in order to monitor local recurrence or distant metastasis.[46]

Since eligibility for certain treatments is modulated by genetic subtype, genomic testing for RAS or BRAF V600E mutations is performed in all people with mCRC who are suitable for systemic treatment, at diagnosis of metastatic disease.[46] In addition, testing for dMMR/MSI-H status is recommended at diagnosis of the primary tumour; this will involve either a test for MSI, or an IHC panel that tests for the loss of expression of four MMR associated proteins (MLH1, MSH2, MSH6 or PMS2).[22] As previously mentioned, these tests are strongly correlated, with a discordance rate of 1.6–3.4%, and so generally only one test is required.[27-29,47] Tests are performed on tumour tissue, which may originate from a biopsy, resected tumour or polyp.[23]

NICE guidelines recommend testing for dMMR/MSI-H status in all cases of CRC.[22] In addition to testing for dMMR/MSI-H, NICE guidelines recommend that tumours that are dMMR/MSI-H positive require sequential testing for other related mutations or for Lynch syndrome, an inherited genetic condition which increases the risk of developing certain cancers such as colon cancer and endometrial cancer.[44,48] Around 20% of dMMR/MSI-H tumours in CRC may be attributable to Lynch syndrome (hereditary CRC), with some real-world studies reporting a prevalence of up to 30%.[49-53] The prevalence also varies strongly with age: in people with dMMR CRC aged < 40, 83% of cases were attributable to Lynch syndrome; in people aged 40–64, this was 25%; and in those aged 65–69, this was 4.8%.[53]

Testing rates have increased over the past few years, with 94% of people diagnosed with CRC or endometrial cancer receiving the test for Lynch syndrome in 2021-2023,

up from 47% in 2019.[54] It is especially important that patients with late-stage disease receive timely screening results in order to start treatment before their disease develops further.

B.1.3.1.3 Staging and classification

The most common way of staging CRC is tumour/node/metastasis (TNM) staging.[55] According to the TNM staging system, mCRC may be classed as any of the stages shown in black in Table 3.

Table 3. TNM staging system

Tumour (T)		Node (N)		Metastases (M)	
Tis	Tumour is only in the mucosa	N0	No lymph nodes containing cancerous cells	M0	cancer is localised
T1	Tumour is localised to the inner layer of the bowel	N1	a – cancer has spread to **one** nearby lymph node	M1	a – cancer has spread to **one** distant site, but has not spread to the peritoneum
T2	Tumour has grown into the muscle of the bowel wall		b – cancer has spread to **two or three** nearby lymph node		b – cancer has spread to **two or more** distant sites, but has not spread to the peritoneum
T3	Tumour has grown into the outer lining of the bowel wall		C – cancer has not spread to nearby lymph notes, but there are cancerous cells in the tissue surrounding the tumour		c – cancer has spread to the peritoneum
T4	a – Tumour has spread to the peritoneum	N2	a – cancer has spread to **four to six** nearby lymph nodes		
	b – Tumour has metastasised to nearby organs		b – cancer has spread to **more than seven** nearby lymph nodes		

In addition, there is the Duke staging system, or number staging (Table 4). In this staging system, mCRC corresponds to Duke's D or stage IV.

Table 4. Duke staging system

Duke's A / Stage I	Tumour is localised to the inner layer of the bowel wall, or has grown into the muscle layer
Duke's B / Stage II	Tumour has grown through the muscle layer of the bowel wall
Duke's C / Stage III	Cancer has spread to at least one lymph node close to the bowel
Duke's D / Stage IV	Cancer has spread to a distant site

B.1.3.1.4 Clinical presentation and symptoms

Symptoms of CRC may be both localised and generalised, and depend on the site(s) of metastasis. General symptoms include anaemia, tiredness, reduced appetite, weight loss, and breathlessness, whilst localised symptoms of the primary tumour may include rectal bleeding, diarrhoea or constipation, abdominal pain, or pain in the lower back. In addition, an obstructed bowel may present with symptoms such as abdominal cramping and pain, bloating, constipation and vomiting.[45,56] Symptoms of hepatic metastases may include pain on the right side of the abdomen, abdominal swelling, nausea, poor appetite and jaundice, whilst lung metastases may present with coughing, breathlessness, pleural effusion, and haemoptysis.[6]

A prospective study of 2,507 patients referred for suspicion of CRC in England found that the most common initial symptoms reported were 'change in bowel habit' (43.4%) and rectal bleeding (34.2%), and that over half (53.1%) had a solitary first symptom. Less specific first symptoms, such as fatigue (23.0%) or 'feeling different' (17.8%), were also often reported.[57] Existing gastrointestinal (GI) comorbidities and mental health diagnoses were associated with longer time to diagnosis;[57,58] in addition, patients aged 45 years or younger may experience a longer wait before

diagnosis, due to the rarity of CRC in this age group.[58,59] However, it is important to note that the relationship between diagnostic interval and age is not linear, and people aged 85 or older may also experience a longer time to diagnosis, potentially due to a higher degree of comorbidity.[59,60]

Potentially as a result of non-specific symptom presentation, and delay in patients presenting to primary care, CRC is often diagnosed at an advanced stage; as mentioned above, 22.7% of all CRC diagnoses in England between 2016 and 2020 were already at the metastatic stage (Table 5).[43,57]

Not all cases of mCRC are metastatic at diagnoses; in some cases, the cancer is diagnosed at an earlier stage and becomes metastatic after progressing. However, UK observational studies have found that ≥ 70% of mCRC cases were diagnosed at stage IV (metastatic at diagnosis), and around 30% of patients presented with multiple metastases.[12-14]

Table 5. CRC diagnoses in England in 2016-2020, stratified by stage at diagnosis

	Total	**Stage at diagnosis**					
		1	2	3	4	Un-stageable	Un-known
Male	95,200	16,141 (17.0%)	21,159 (22.2%)	26,178 (27.5%)	21,588 (22.7%)	47 (0.1%)	10,087 (10.6%)
Female	75,569	11,477 (15.2%)	17,144 (22.7%)	20,112 (26.6%)	17,141 (22.7%)	43 (0.1%)	9,652 (12.8%)

Abbreviations: CRC, colorectal cancer

The NHS currently offers screening via FIT, which replaced the guaiac-based faecal occult blood test (gFOBT) in 2016. Screening is offered every two years, to those aged 60–74;[61] In Scotland, England and Wales, this has been or is being expanded to people in their 50s.[62] In the first 10 years of the testing programme (2006–2016), uptake was only 56%; however, the introduction of the easier-to-use FIT increased uptake to around 62–70% across the UK.[63] However, there are still barriers to participation. Psychological barriers to screening participation include: fear about the

test outcome, the idea that the test is not applicable if you don't have symptoms, or perception that the risk of CRC is low. In addition, certain groups may be less likely to participate, including: men, those of lower socioeconomic status, people from non-white ethnic backgrounds, and people for whom English is not their first language.[63]

Data from the English National Cancer Registry showed that in 2014, 26.5% of colon cancers were diagnosed in an emergency setting and 41.1% were diagnosed via an urgent two-week referral, whilst only 7.6% were diagnosed through routine care and 9.2% through the national screening programme.[64] 1-year OS for CRC detected through screening is as high as 97% but, when detected in an emergency setting, this drops to only 49%.[61] These data must be interpreted cautiously as FIT was not introduced until 2016.

B.1.3.2 Current pathway of care and treatment guidelines

In CRC, choice of systemic therapy depends on genetic subtype, disease severity and extent of previous treatment. Treatment often includes surgery and may include targeted therapies such as selective internal radiation therapy (SIRT). In unresectable stage III (Duke's C) CRC, first-line options for systemic treatment include fluoropyrimidine-based chemotherapy (FOLFOX, FOLFIRI) or capecitabine monotherapy; however, capecitabine is rarely used in clinical practice.[1,2] In dMMR/MSI-H CRC, NIVO + IPI may be given after fluoropyrimidine-based chemotherapy; pembrolizumab (PEMBRO) may be given if NIVO + IPI is not suitable.[65]

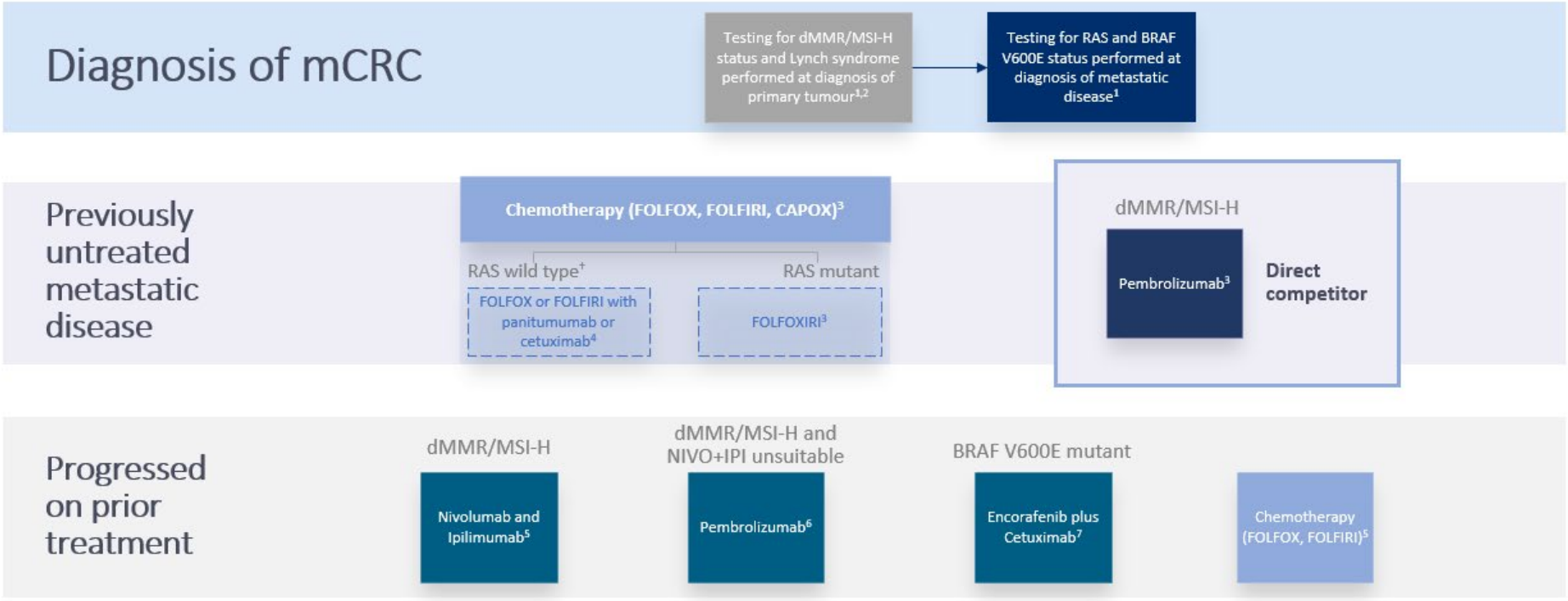
PEMBRO is currently the only treatment specifically recommended by NICE for the systemic treatment of adult patients with previously untreated mCRC with dMMR/MSI-H.[1] PEMBRO is a humanised monoclonal anti-PD-1 antibody with a similar mechanism of action to nivolumab, binding to the PD-1 receptor and blocking interaction with the ligands, PD-L1 and programmed death ligand 2 (PD-L2).[66] PEMBRO was first approved by the European Medicines Agency (EMA) in 2015 for the treatment of advanced melanoma. In 2020, the marketing authorisation was expanded to include 1L treatment of mCRC with dMMR/MSI-H.[67,68] ESMO guidelines also recommend PEMBRO as first choice for 1L therapy in mCRC with dMMR/MSI-H.[48]

In the pivotal KEYNOTE-177 (KN-177) trial, PEMBRO was associated with a disease control rate (DCR) of 64.7%, with 29.4% of patients having a best response of progressive disease (PD); in the chemotherapy group, this was 75.3% and 12.3%.[1,69] Hence, chemotherapy may still be considered more suitable in patients with very advanced disease, in whom progression would rule out further treatment.

In this case, people with untreated dMMR/MSI-H mCRC are usually offered fluoracil-folinic acid- or capeticabine-based combination chemotherapy (FOLFOX, FOLFIRI or CAPOX).[1] For RAS wild-type mCRC, cetuximab or panitumumab may be added to FOLFOX or FOLFIRI, and for RAS mutant mCRC, a triple combination regimen may be considered (FOLFOXIRI).[1,70]

Figure 2 presents a summary of the clinical pathway for mCRC and main comparators for NIVO + IPI.

Figure 2. Systemic treatment options for metastatic colorectal cancer[1,46,65,71-75]



†Cetuximab is only an option for epidermal growth factor receptor (EGRF) expressing tumours

Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficiency; EGFR, epidermal growth factor receptor; MSI-H, microsatellite instability high

References: 1. NG151–- Colorectal cancer. https://www.nice.org.uk/guidance/ng151. 2. NICE: Molecular testing strategies for Lynch syndrome. https://www.nice.org.uk/guidance/dg27 3. NICE TA709 https://www.nice.org.uk/guidance/ta709 4. NICE TA439 https://www.nice.org.uk/guidance/ta439 5. NICE TA716 https://www.nice.org.uk/guidance/ta716 6. NICE TA914 https://www.nice.org.uk/guidance/ta914 7. NICE TA668

Treatment for mCRC is also modulated by metastatic pattern (Table 6).

Table 6. NICE guidelines for the treatment of metastases in mCRC

Liver	Consider resection, either simultaneous or sequential, after discussion by a multidisciplinary team with expertise in resection of disease in all involved sites Consider perioperative systemic anti-cancer therapy if liver resection is a suitable treatment Consider chemotherapy with local ablative techniques for people with colorectal liver metastases that are unsuitable for liver resection after discussion by a specialist multidisciplinary team *Do not offer selective internal radiation therapy as 1L treatment for people with colorectal liver metastases that are unsuitable for local treatment.*
Lung	Consider metastasectomy, ablation or stereotactic body radiation therapy for people with lung metastases that are suitable for local treatment, after discussion by a multidisciplinary team that includes a thoracic surgeon and a specialist in non-surgical ablation. Consider biopsy for people with a single lung lesion to exclude primary lung cancer.
Peritoneum	Offer systemic anti-cancer therapy and within a multidisciplinary team, discuss referral to a nationally commissioned specialist centre to consider cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Abbreviations: 1L, first-line; mCRC, metastatic colorectal cancer

B.1.3.3 Nivolumab and Ipilimumab: Mechanism of action

NIVO and IPI are ICIs with different targets, leading to a synergistic response when used together.[3-5,76]

NIVO potentiates T-cell responses by binding to PD-1, thereby blocking its binding to the PD-L1 and PD-L2 ligands. PD-1 is a negative regulator of T-cell activity, and since the ligands PD-L1 and PD-L2 are commonly upregulated on the surface of solid tumours, the unregulated PD-1 pathway results in inhibition of the cytotoxic immune response that would normally attack cancer cells.[35,77] PD-1 blockade therefore enables T-cells to recognise and attack cancer cells more effectively, and ICIs targeting the PD-1 pathway have achieved impressive results across multiple

cancer types.[5] In mCRC, the presence of dMMR is a strong positive predictor of response to PD-1 blockade. This may be due to the increased infiltration of immune cells in dMMR tumours, and associated cytokine-rich microenvironment.[18,35,36] Additionally, in dMMR/MSI-H tumours, high TMB is an independent predictor of response to ICIs.[39]

IPI is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway. CTLA-4 is a key negative regulator of the early stages of T-cell activation, primarily at sites of T-cell priming.[77,78] CTLA-4 competes with costimulatory molecule, cluster of differentiation 28 (CD28) for the ligands CD80 and CD86, for which it has a higher affinity.[79] When bound to CD80/86, CTLA-4 transmits inhibitory signals to prevent CD28-mediated T-cell activation.[80] In addition, CTLA-4 attenuates T-cell activation in peripheral tissues.[81]

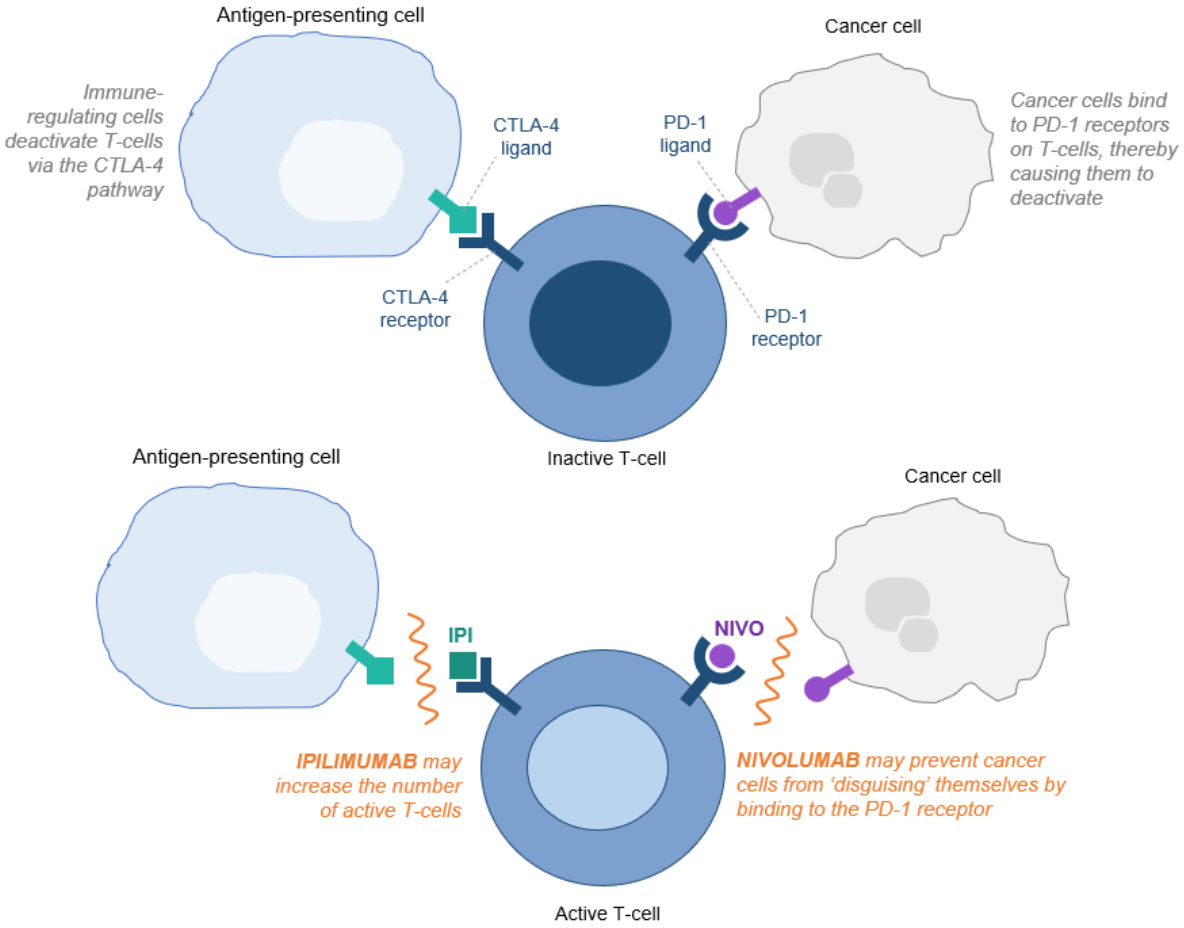
Thus, CTLA-4 blockade increases the number of reactive effector T-cells (cells that are programmed to attack pathogens).[4,82] CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. IPI may also selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intra-tumoural T-effector/ T-regulatory cell ratio, driving tumour cell death.[3,4]

Combination therapy leads to a synergistic response,[3-5,76] in which CTLA-4 blockade increases the number of effector T-cells in the tumour environment, whilst PD-1 blockade enables T-cells to recognise and attack cancer cells (Figure 3). This leads to improved long-term survival outcomes.

In CheckMate 067, a double-blind randomised controlled trial (RCT) comparing NIVO + IPI with NIVO monotherapy and IPI monotherapy in advanced melanoma, combination therapy demonstrated statistically superior OS versus IPI monotherapy. At a follow-up of 60 months, OS was not reached in the combination therapy group; for NIVO monotherapy it was 36.9 months, and in the IPI monotherapy group it was 19.9 months. The hazard ratio (HR) for death for NIVO + IPI vs. IPI monotherapy was 0.52, significantly in favour of combination therapy. Likewise, the median progression-free survival (PFS) was 11.5 months for NIVO + IPI, 6.9 months for NIVO and 2.9 months for IPI.[83]

This has also been explored in previously-treated MSI-H mCRC. In the CheckMate 142 trial, the addition of IPI to NIVO monotherapy resulted in observed improvements in ORR (39% vs. 65%), 5-year PFS (34% vs. 52%) and 5-year OS (46% vs. 68%).[84] However, no statistical comparison was conducted. This has been observed across other indications, in real world evidence and indirect comparisons.[85,86]

Figure 3. How the combination of nivolumab and ipilimumab works: reproduced from Opdivo website[76]



Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen-4; IPI, ipilimumab; NIVO, nivolumab; PD-1, programmed death-1

B.1.3.4 Burden and unmet needs

Patients with CRC experience a severe symptom burden, resulting from both the disease and from treatment toxicity. Patients describe experiencing fatigue, GI symptoms, neuropathy, loss of appetite, weight loss and abdominal pain, which

affect their ability to work, sleep, do their usual daily activities, have a social life, and in some cases, walk.[87-89] In addition, one prospective observational study found that MSI-H status was associated with greater symptom burden, with an increased incidence of pain (odds ratio [OR] 3.06), fatigue (OR 2.78), and sleep disturbance (OR 2.52) compared with MSS mCRC tumours.[90]

Survival in CRC is poor when diagnosed at a late stage; the 5-year OS for those diagnosed at stage IV is less than 20%.[12,13,43] A recent UK observational study found that median OS for patients with mCRC receiving 1L chemotherapy was 17.8 months, demonstrating an unmet need for additional treatment options.[91]

Further, the dMMR/MSI-H subtype is associated with poorer prognosis compared with mismatch repair proficient (pMMR)/MSS tumours. In international observational studies, dMMR/MSI-H tumours have demonstrated a response rate at least 4-fold lower than pMMR/MSS tumours, reducing OS by 5–9 months across treatment lines.[7,33,92-94] Median OS for patients with dMMR/MSI-H mCRC treated with 1L chemotherapy (with or without monoclonal antibodies) ranges from 16 to 36 months;[69,95-98] liver metastases, the most common metastatic site, are also associated with poorer PFS and tumour response.[99-101]

These inferior outcomes are associated with the reduced chemosensitivity of dMMR/MSI-H tumours, demonstrating inferior response to commonly-used treatments such as fluorouracil- and oxaliplatin-based regimens including FOLFOX and CAPOX.[7,26,92,102,103] In particular, chemotoxicity induced by fluorouracil may be mediated by the MMR pathway, and preclinical studies have shown that dMMR CRC cell lines are at least 18-fold more resistant to fluorouracil than pMMR cell lines.[93] By contrast, MSI-H tumours show promising response to immunotherapies (IO).[18,24,35,36,104]

PEMBRO is currently the only treatment specifically approved and recommended by NICE for the 1L dMMR/MSI-H population;[1] however, this treatment has some limitations. In the pivotal KN-177 trial, a higher proportion of patients in the PEMBRO arm had a best response of PD compared with the chemotherapy arm (29.4% vs. 12.3%), with a lower DCR (64.7% vs. 75.3%). Additionally, the 6-month PFS rates were similar between PEMBRO and chemotherapy (57.6% and 59.7%), with the

PEMBRO curve reaching a plateau at 40–50%, resulting in a median PFS of 16.5 months.[1,69] Hence, there is an unmet need for an IO that offers better long-term survival outcomes and sustained PFS benefits.

In addition, PEMBRO has not demonstrated benefit in specific subgroups; in KN-177, the HR for PFS did not favour PEMBRO in those aged > 70, people with an Eastern Cooperative Oncology Group Performance Score (ECOG PS) of 1, people with left-sided tumours, and people with KRAS or NRAS mutations.[1,69] Hence, there is an unmet need for an IO with demonstrated PFS benefits across all patient groups.[16]

Current treatments for mCRC are associated with a considerable adverse event (AE) burden, which also impacts on patients' functioning.[105,106] KN-177 details common AEs associated with 1L chemotherapy and with PEMBRO in previously-untreated dMMR mCRC. Treatment with chemotherapy was associated with a higher proportion of treatment-related adverse events (TRAEs) compared with PEMBRO (99% vs. 80%, respectively), and a higher proportion of grade ≥ 3 TRAEs (66% vs. 22%) and serious TRAEs (29% vs.16%). The most frequent grade ≥ 3 TRAEs associated with chemotherapy included decreased neutrophil count, neutropenia, diarrhoea and fatigue, whilst the most frequent AEs in the PEMBRO group included increased alanine aminotransferase, colitis, diarrhoea, and fatigue.[69] Immunotherapy-specific AEs, including hypothyroidism, colitis, pneumonitis, adrenal insufficiency and hepatitis occurred in 30.7% of participants in the PEMBRO arm, with serious immunotherapy-specific AEs occurring in 10.5%, and 6.5% of participants discontinuing treatment due to immunotherapy-specific AEs. Of the 65 total immunotherapy-specific AEs, 23.1% were treated with high-dose corticosteroids.[69]

In general, however, IOs are associated with improved quality of life (QoL) compared with chemotherapy.[107] Using data from KN-177, Andre et al.[108] found that chemotherapy was significantly associated with worse QoL than IOs. Across the study period, scores in physical and social functioning declined in the chemotherapy group and improved in the PEMBRO group. Whilst this may be partially explained by poorer long-term PFS in the chemotherapy group, this group also saw declines in

symptom scores including fatigue, nausea and vomiting, appetite loss, and diarrhoea, which are all characteristic AEs linked to chemotherapy.[106,108] This infers that there is a severe AE burden associated with chemotherapy for dMMR/MSI-H mCRC. In addition, epidermal growth factor receptor (EGFR) inhibitors (panitumumab, cetuximab) are associated with characteristic AEs such as skin reactions.[7,26,92,102,109,110] Hence, there remains an unmet need for an IO which provides an additional alternative to chemotherapy, whilst maintaining a manageable safety profile.

CRC is a highly prevalent cancer, for which survival is poor in the advanced stages, exacerbated by the problem of poor screening uptake and late diagnosis.[43,63] The dMMR/MSI-H subtype represents a distinct population of patients with unique treatment needs, defined by markedly reduced chemosensitivity and consequently, inferior outcomes.[7,33,92-94] Though PEMBRO represents a step forward, it has limitations, in that it is still associated with fairly short median PFS (16.5 months), with a PFS rate of ~40% at 36 months of follow-up.[1] Hence, there is still an unmet need for an efficacious treatment which will provide strong and sustained survival benefits compared with chemotherapy.

B.1.3.5 Place in pathway

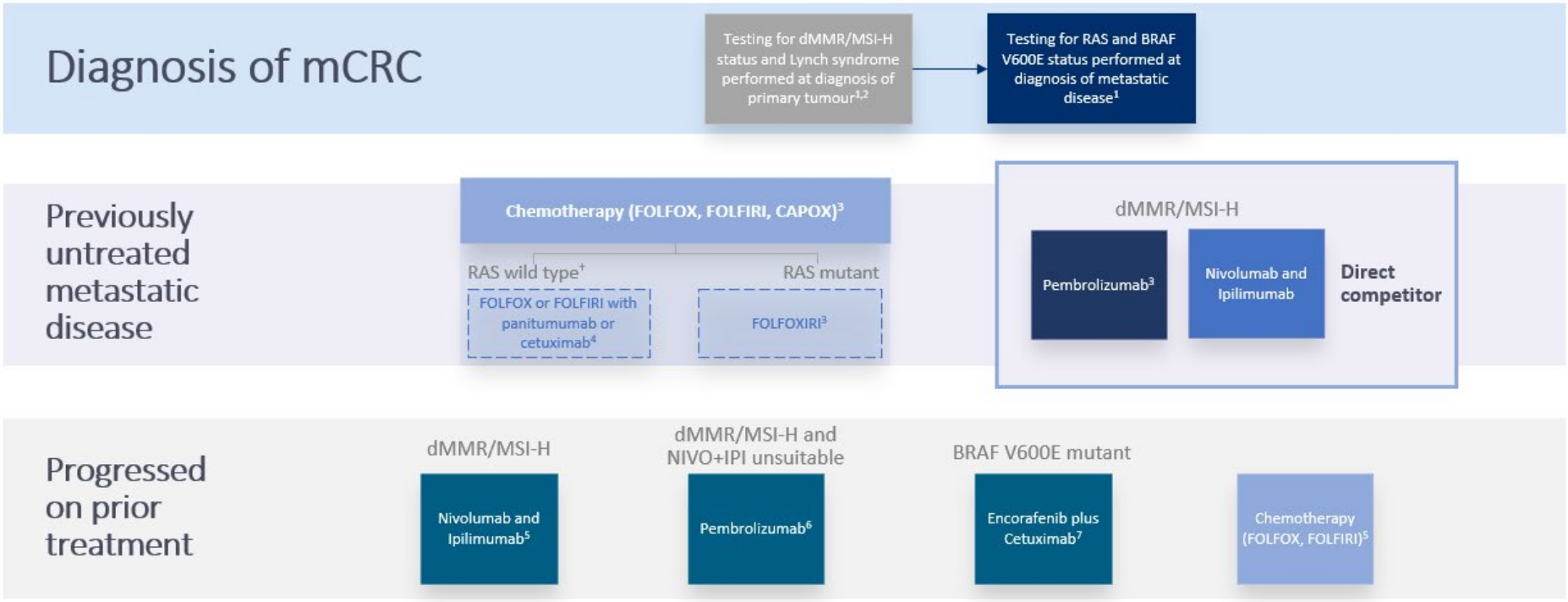
It is anticipated that NIVO + IPI will be indicated for the treatment of adults and adolescents with previously-untreated unresectable or metastatic CRC with dMMR/MSI-H.

In the population with untreated dMMR/MSI-H mCRC, it will provide an alternative to PEMBRO, which is currently the only other treatment recommended in this indication; in the population with unresectable dMMR/MSI-H CRC, it will present an alternative to oxaliplatin-based chemotherapy and will represent the first combination therapy to be approved specifically for dMMR/MSI-H tumours.

Although the key clinical trials included adult populations, a pharmacokinetic (PK) simulation study concluded that the exposure of the proposed dosing regimen for both NIVO and IPI in adolescents is expected to result in comparable benefits and risks to those in adults.[111]

Therefore, NIVO + IPI represents an opportunity to address a significant unmet need. Through a synergistic mechanism of action, NIVO + IPI offers meaningful improvements in patient survival and progression and similar safety profile compared with PEMBRO.

Figure 4. Place in pathway of nivolumab plus ipilimumab[1,46,65,71-75]



Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficiency; EGFR, epidermal growth factor receptor; MSI-H, microsatellite instability high

References: 1. NG151. Colorectal cancer. https://www.nice.org.uk/guidance/ng151. 2. NICE: Molecular testing strategies for Lynch syndrome. https://www.nice.org.uk/guidance/dg27 3. NICE TA709 https://www.nice.org.uk/guidance/ta709 4. NICE TA439 https://www.nice.org.uk/guidance/ta439 5. NICE TA716 https://www.nice.org.uk/guidance/ta716 6. NICE TA914 https://www.nice.org.uk/guidance/ta914 7. NICE TA668

B.1.4 Equality considerations

It is not considered that this appraisal will exclude any people protected by equality legislation; or lead to a recommendation that would have a different impact on people protected by equality legislations than on the wider population; or lead to recommendations that would have an adverse impact on people with a particular disability.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify clinical effectiveness evidence (efficacy and safety) regarding interventions for the 1L treatment of recurrent or metastatic CRC.

Searches were originally run on June 15, 2021, and updated searches were run on 10 May 2024. Relevant studies were identified by searching the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE, via OvidSP), Excerpta Medica dataBASE (Embase, via OvidSP), Cochrane Database of Systematic Reviews (CDSR), Cochrane Controlled Register of Trials (CENTRAL). Conference proceedings from 2022–2024 were searched, to identify relevant publications which may not have been indexed on Embase: American Association for Cancer Research (AACR), American Society of Clinical Oncology (ASCO), ASCO gastrointestinal cancers symposium, American Society of Colon and Rectal Surgeons (ASCRS), European Society of Coloproctology (ESCP) and European Society for Medical Oncology (ESMO). In addition, grey literature searches were carried out by hand in order to capture relevant publications not indexed in these databases. Grey literature searches included the United States and European clinical trials registry databases. Additionally, bibliographies of recent and relevant systematic reviews published in the last three years (2021–2024) were searched. Full details of the methods and processes employed to identify and select the relevant clinical evidence are summarised in Appendix D.

The updated SLR identified 1,696 titles and abstracts after de-duplication. Following full text screening, 120 records were retrieved and 104 excluded. Thus, 16 publications were included in the review. A further 9 records were identified through supplemental searches; of these, 3 had already been picked up in database searches, and 4 were excluded, leaving 2 to be included in the review (Figure 5).

In total, four unique trials described in 18 publications met the eligibility criteria for inclusion in the SLR (Table 7).

Figure 5. PRISMA diagram for systematic literature review

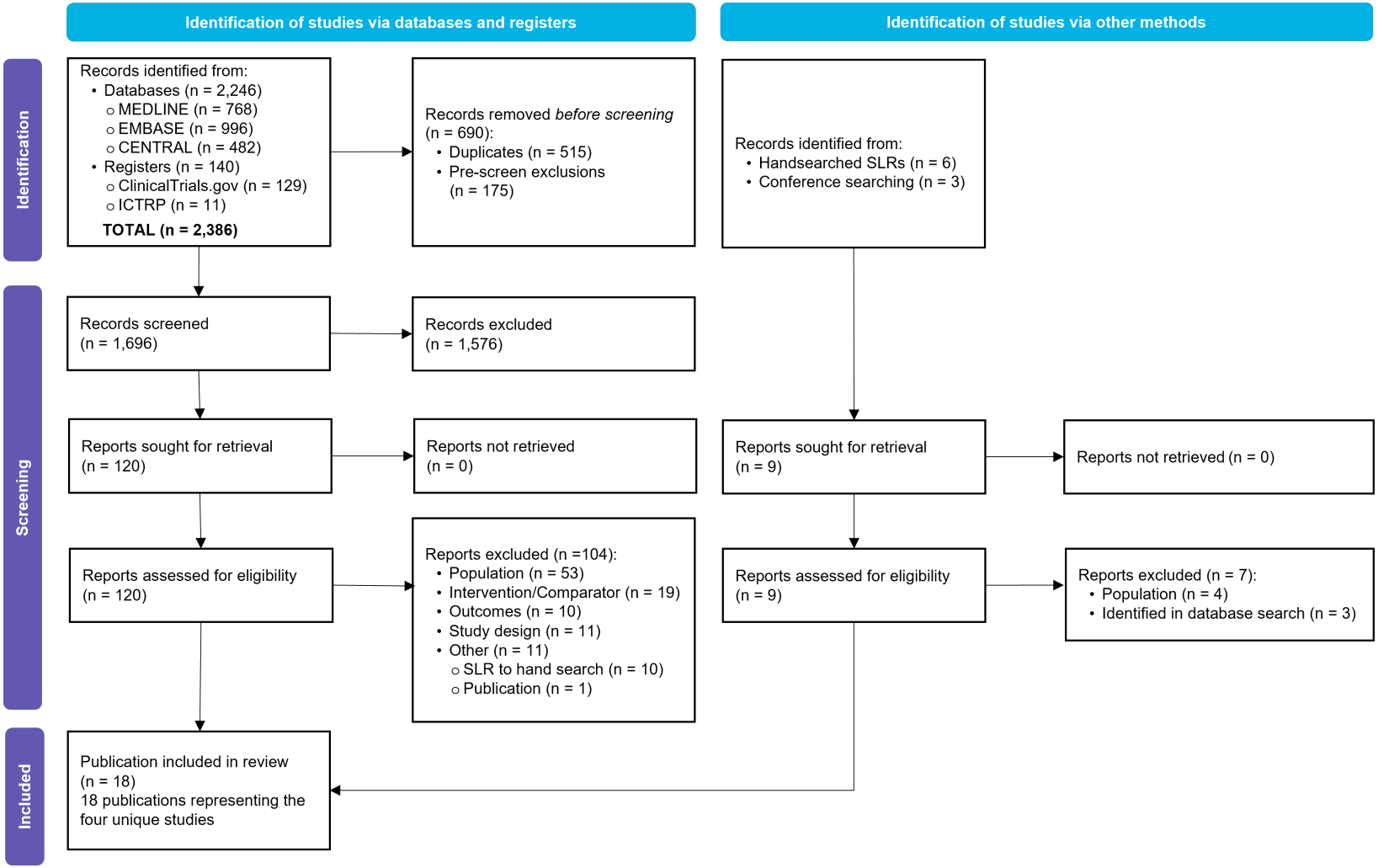


Table 7. Characteristics of studies included in SLR

Study	Design	Study country	Patient population	Treatment arms
CheckMate 142 (NCT02060188)	Phase 2 non-randomised multi-cohort trial	Australia, Belgium, Canada, France, Ireland, Italy, Spain, USA	**Cohort 3:** untreated MSI-H mCRC (n=45)	NIVO + IPI
CheckMate 8HW (NCT04008030)	Phase 3 RCT	Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Czechia, Denmark, France, Germany, Greece, Ireland, Italy, Japan, Netherlands, Norway, Puerto Rico, Romania, Spain, Turkey, United Kingdom, USA	Untreated dMMR/MSI-H mCRC (n=303)	• NIVO + IPI • Investigator's choice of chemotherapy (FOLFIRI or mFOLFOX ± bevacizumab or cetuximab)
KEYNOTE-177 (NCT02563002)	Phase 3 RCT	Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, USA	Untreated dMMR/MSI-H mCRC (n=307)	• PEMBRO • Investigator's choice of chemotherapy (FOLFIRI or mFOLFOX ± bevacizumab or cetuximab)
CALGB/SWOG 80405 [Alliance] (NCT00265850)	Phase 3 RCT	Canada, USA	Untreated, locally advanced or metastatic MSI-H CRC (n=15)	FOLFOX or FOLFIRI ± cetuximab

Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficient; IPI, ipilimumab; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability high; NIVO, nivolumab; PEMBRO, pembrolizumab; RCT, randomised controlled trial

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Summary of clinical effectiveness evidence

CM8HW was identified as the sole trial that provided clinical effectiveness evidence for NIVO + IPI in patients with previously untreated dMMR/MSI-H mCRC, with reference to a relevant comparator. CM8HW is an ongoing, phase 3, multicentre, open-label, parallel-group randomised trial investigating the efficacy and safety of NIVO + IPI, compared with either NIVO monotherapy or chemotherapy (investigator's choice), across all treatment lines and for 1L. This submission will focus on the 1L population in the NIVO + IPI and chemotherapy arms. Since CM8HW is ongoing, future analysis will provide longer-term efficacy and safety evidence.

In addition, CM142 was identified as a non-comparative trial providing long-term clinical effectiveness evidence (64-month follow-up) for NIVO + IPI in patients with previously untreated MSI-H mCRC. The study consisted of 6 mCRC cohorts, as outlined in Table 8. In this submission, the results of Cohort 3, which investigated NIVO + IPI the population of interest (1L MSI-H mCRC), are presented. As the survival data in CM8HW are less mature (32-month follow-up), this submission presents CM142 as supportive evidence.

A summary of the two trials is provided in Table 9.

Table 8. Dose regimens in CM142 study cohorts

Cohort	Regimen	Line of therapy	MSI-H?
1	NIVO 3mg/kg Q2W	2L+	Y
2	NIVO 3mg/kg + IPI 1mg/kg Q3W x4 **then** NIVO 3mg/kg Q2W	2L+	Y
3	NIVO 3mg/kg Q2W + IPI 1mg/kg Q6W	1L	Y
4	NIVO 3mg/kg Q2W + IPI 1mg/kg Q6W + Cobimetinib 60mg OD 21 days on/7 days off	2L+	N
5	NIVO 240mg Q2W + Relatlimab 160mg Q2W	2L+	Y
6	NIVO 240mg Q2W starting on Week 3, then Q4W starting on Week 25, **and** Daratumumab 16mg/kg Q1W starting on Week 1, Q2W week 9-24, then Q4W on Week 25	2L+	N

Abbreviations: 1L, first-line; 2L, second-line; IPI, ipilimumab; MSI-H, microsatellite instability high; NIVO, nivolumab; OD, once daily; Q2W, every 2 weeks; Q3W, every 3 weeks, Q4W, every 4 weeks, Q6W, every 6 weeks

Table 9. Summary of CM8HW and CM142

Trial name	CM8HW	CM142 Cohort 3
Trial design	Phase 3, multicentre, open-label, randomised, parallel-group study	Phase 2, multicentre, open-label, non-randomised single-arm study
Population	Histologically confirmed unresectable or metastatic CRC, with MSI-H/dMMR status by local testing and ECOG PS 0 or 1	Histologically confirmed unresectable or metastatic CRC, with MSI-H/dMMR status by local testing and ECOG PS 0 or 1
Location	88 investigational sites in 22 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czechia, Denmark, France, Germany, Greece, Ireland, Italy, Japan, Netherlands, Romania, Spain, Turkey, UK, and US) Among 303 randomised subjects, 204 were from the US/Canada/Europe	18 investigational sites in 6 countries (Australia, Belgium, Ireland, Italy, Spain, USA)
Intervention(s)	NIVO 240mg + IPI 1mg/kg every 3 weeks for 4 doses, followed by NIVO 480mg every 4 weeks, for a maximum of 2 years	NIVO 3mg/kg + IPI 1mg/kg administered together on day 1 of cycle 1 and then once every 2 weeks (NIVO) or once every 6 weeks (IPI)
	NIVO 240mg every 2 weeks for 6 doses, followed by NIVO 480mg every 4 weeks, for a maximum of 2 years	
Comparator(s)	Investigator's choice of chemotherapy (mFOLFOX or FOLFIRI ± bevacizumab or cetuximab)	N/A
Randomisation scheme	Patients were randomised in a 2:2:1 ratio. Randomisation to the chemotherapy arm is restricted to patients who had received no more than 1 prior line of systemic therapy	N/A
Stratification factors	• Number of prior lines of treatment (1L, 2L, 3L+). Only 1L is presented. • Primary tumour location (left/right)	N/A
Indicate if study supports application	Yes	Yes

Company evidence submission for nivolumab with ipilimumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.

Trial name	CM8HW	CM142 Cohort 3
for marketing authorisation		
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A
Primary endpoint	PFS per BICR in centrally confirmed dMMR/MSI-H population (all lines and 1L)	ORR by investigator (This was further characterised by DOR and CRR by investigator)
Secondary endpoints	• PFS per BICR in all randomised subjects, and centrally confirmed dMMR/MSI-H population by each central test (all lines and 1L) • PFS per investigator in centrally confirmed population (1L only) • ORR by BICR in centrally confirmed population (all lines and 1L) • OS in centrally confirmed population (all lines and 1L) • PFS and ORR by BICR in crossover cohort	• ORR by BICR • DOR and CRR by BICR • DCR by investigator and by BICR
Exploratory endpoints	• Association of biomarkers with efficacy in all randomised participants • PFS2 per investigator in centrally confirmed population • RFS and TTF per investigator in centrally confirmed population • Safety and tolerability in all treated subjects (deaths, AEs, SAEs, select AEs, IMAEs, OESIs, lab abnormalities) • EORTC QLQ-CR30 and QLQ-CR29 scores and EQ-5D VAS and utility scores in all randomised subjects • Immunogenicity and PK in all NIVO or NIVO + IPI treated subjects	• Safety and tolerability (deaths, AEs, SAEs, lab abnormalities) • PFS by investigator and by BICR • OS by investigator and by BICR • Pharmacokinetics • Immunogenicity • Association of biomarkers with efficacy • Pharmacogenomics • EQ-5D score, EORTC QLQ-C30 score

Trial name	CM8HW	CM142 Cohort 3
	• ORR and PFS by investigator, OS, safety profile, and PK/immunogenicity in crossover cohort	• Discordance rate between repeat MSI testing and prior MSI testing • Endpoints for re-initiation cohort (BOR, ORR, DCR, TTR, DOR, PFS, OS)
Pre-specified subgroups for primary endpoint	• Age (< 65, ≥ 65 and < 75, ≥ 75 and < 85, ≥ 85, ≥ 75, ≥ 65) • Sex (Male, Female) • Race (White, Black or African American, Asian, Other) • Ethnicity (Hispanic/Latino, Not Hispanic/Latino) • Region (US/Canada/Europe, Asia, Rest of World) • ECOG PS (0, ≥ 1) • Tobacco use (Yes, No, Not Reported) • Alcohol use (Yes, No, Not Reported) • Disease stage at initial diagnosis (Stage 0, I, II, III, IV) • Cell type (Adenocarcinoma, Other types) • Tumour location (Cecum, Colon Ascending/Hepatic Flexure, Colon Transverse, Colon Descending/Splenic Flexure, Colon Sigmoid, Rectum/Rectosigmoid Junction, Unknown) • Tumour sidedness (Left, Right) • Time from initial disease diagnosis to randomisation (< 1 year, ≥ 1 and ≥ 3 years) • Liver metastasis per BICR (Yes, No, Not Reported) • Lung metastasis per BICR (Yes, No, Not Reported) • Peritoneal metastasis per BICR (Yes, No, Not Reported) • PD-L1 status (≥ 1%, 1<1%, non-quantifiable) • IHC test results per central assessment (dMMR, pMMR, Not Available) • IHC test results per local assessment (dMMR, pMMR, Not Available)	• Age (< 65, ≥65, 65-75, 65, ≥75) • Region (US/Canada, Europe, Rest of World) • Gender (Male, Female) • Race (white, black, Asian, and other) • Lynch syndrome (yes/no) • KRAS and BRAF wild-type, KRAS mutation, BRAF mutation • ECOG (0, 1) • Time from the initial diagnosis to first dose of NIVO (1, 2, 3, 3+ years)

Trial name	CM8HW	CM142 Cohort 3
	• PCR test results per central assessment (MSI-H, MSS, Not Available) • PCR test results per local assessment (MSI-H, MSI-L/MSS, Not Evaluable, Not Tested) • B-RAF, K-RAS, N-RAS mutation status (B-RAF, K-RAS, N-RAS All Wild Type, B-RAF Mutant, K-RAS or N-RAS Mutant, BRAF and KRAS/NRAS Mutant, Unknown) • Lynch syndrome (Yes, No, Unknown) • Prior surgery (Yes, No) • Prior radiotherapy (Yes, No)	

1L, first line; 2L, second line; 3L, third line; AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CRC, colorectal cancer; CRR, complete response rate; DCR, disease control rate; dMMR, mismatch repair deficient; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire; EQ-5D, EuroQol 5-dimensions; IHC, immunohistochemistry; IMAE, immune-mediated adverse events; IPI, ipilimumab; MSI-H, microsatellite instability high; NIVO, nivolumab; OESI, other events of special interests; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RFS, relapse-free survival; SAE, serious adverse event; TTF, time to treatment failure; VAS, visual analogue scale

B.2.3 CheckMate 8HW

B.2.3.1 Summary of methodology

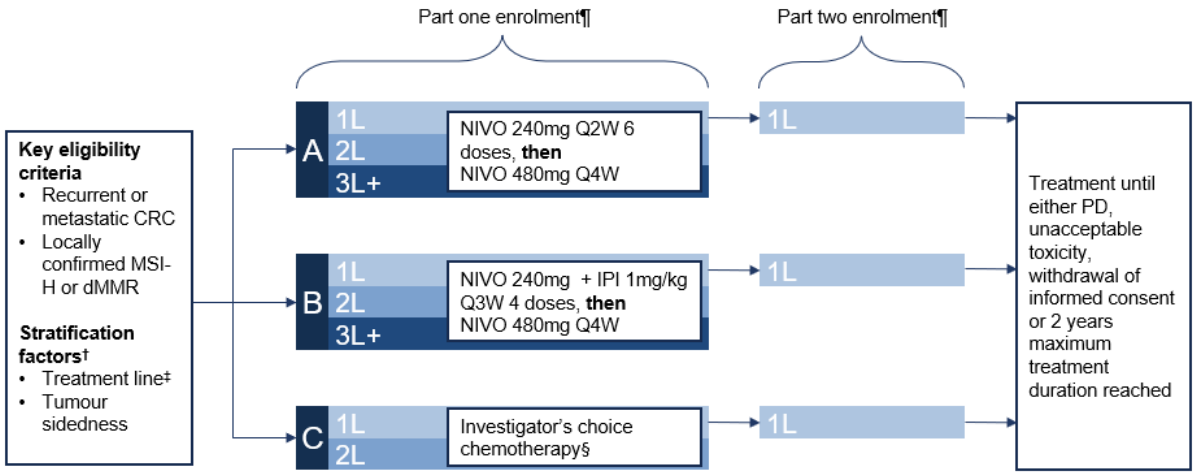
CM8HW is a phase 3, open-label, parallel group study investigating the efficacy and safety of NIVO monotherapy, NIVO + IPI combination therapy, and chemotherapy (investigator's choice) in the treatment of mCRC with confirmed dMMR/MSI-H status, across all treatment lines and for 1L. Chemotherapy regimens included mFOLFOX6 or FOLFIRI, with or without bevacizumab or cetuximab.

CM8HW had two enrolment periods, with the second encompassing only patients who had not previously received therapy. Patients were then randomised to NIVO monotherapy, NIVO + IPI or chemotherapy in a 2:2:1 ratio; randomisation to the chemotherapy arm is restricted to the 1L/2L population. Patients assigned to chemotherapy who experienced disease progression per RECIST v1.1 had the option to crossover to NIVO + IPI, albeit on a different dosing schedule, provided they met all crossover criteria as outlined in the summary table (Table 10). The crossover cohort received treatment for the same duration as those randomised to NIVO + IPI, followed the same assessment schedules and were analysed in the same way where feasible.

Patients with metastatic disease were stratified by extent of previous therapy (1L, 2L and 3L+ populations), and by sidedness of tumour (left/right hand side of colon). There is some evidence that right-sided tumours have worse prognoses than left-sided tumours in mCRC,[112] and also that right-sidedness is associated with higher rates of dMMR/MSI-H.[113] In line with the decision problem, this submission presents results from the 1L population in the NIVO + IPI arm and the chemotherapy arm. The primary endpoint is PFS per BICR in 1L randomised patients with centrally confirmed MSI-H/dMMR mCRC (NIVO + IPI vs. chemotherapy); key secondary endpoints are PFS per BICR in all 1L randomised patients (reflecting the full ITT population), and PFS per investigator in 1L randomised patients with centrally confirmed MSI-H/dMMR mCRC.

A schematic of study design is presented in Figure 6, and key inclusion/exclusion criteria are presented in Table 10.

Figure 6. CM8HW study design



Abbreviations: BICR, Blinded Independent Central Review; CRC, colorectal cancer; IC, informed consent, MSI-H, microsatellite instability high; dMMR, deficient mismatch repair; PD, progressive disease; PFS, progression free survival

† Line of therapy is not a stratification factor during Part 2 enrolment; ‡ Participants with ≥2 prior lines are randomized only to arm A or B during Part 1; only participants with 0 prior lines are randomised during Part 2 enrolment; § Optional Crossover for arm C with NIVO + IPI q6w dosing; ¶ Part 1 enrolment continues to allow randomisation of approximately 560 participants across lines of therapy with locally confirmed dMMR/MSI-H mCRC. Part 2 enrolment continues to allow randomization of approximately 271additional participants with locally confirmed dMMR/MSI-H status who have not received prior therapy for metastatic disease (1L). Max treatment duration is not applicable for arm C participants

B.2.3.2 Inclusion/exclusion criteria

Table 10. CM8HW eligibility criteria[114]

Eligibility criteria	• Signed written informed consent form • Histologically confirmed recurrent or metastatic CRC with no prior treatment history with chemotherapy and/or targeted agents for metastatic disease and not amenable to surgery • Participants treated with adjuvant chemotherapy are eligible if disease progression occurred later than 6 months (≥ 6 months) after completion of chemotherapy • Tumour dMMR/MSI-H status confirmed per local practice • Measurable disease by CT/MRI per RECIST v1.1 • Participants with lesion in a previously irradiation field as the sole site of measurable disease are permitted to enrol provided the lesion(s) have demonstrated clear progression and can be measured accurately • Adequate tumour tissue available. Tumour tissue specimens must be submitted to the central laboratory. Sample must be the same one used for dMMR/MSI-H testing • ECOG PS 0 or 1 • Laboratory test findings: WBC ≥ 2000/uL; neutrophils ≥ 1500/uL; platelets ≥ 100 x 10^3/uL; haemoglobin ≥ 9.0 g/dL; PT/INR and PTT ≤ 1.5 x ULN unless receiving anticoagulant therapy and INR is stable and within recommended range; serum creatinine ≤ 1.5 x ULN unless CLCr > 40 mL/min; AST/ALT ≤ 3.0 x ULN, unless participant has documented liver metastases; bilirubin ≤ 1.5 x ULN, except participants with Gilbert syndrome • Aged ≥ 18 years • Women of childbearing potential must have negative pregnancy test and must not be breastfeeding • Women of childbearing potential (WOCBP) who are heterosexually active receiving nivolumab with or without ipilimumab must agree to follow instructions regarding contraception for the duration of treatment with study drugs plus at least 5 months after final dose; for those receiving chemotherapy, this applies 6 months after final dose • Males who are sexually active with WOCBP and who are assigned to receive nivolumab without or with ipilimumab are exempt from contraceptive requirements; as are azoospermic males. Males who are sexually active with WOCBP and who are assigned to receive chemotherapy must agree to follow instructions regarding contraception for the duration of treatment with study drugs and for at least 6 months after final dose

Exclusion criteria	See CSR for full details[114]
Crossover criteria	Participants in the chemotherapy arm who have BICR-confirmed PD during or following receipt of chemotherapy, have the option to receive NIVO + IPI. Crossover is optional and is at the discretion of investigator. The following eligibility criteria are applied: • BICR-confirmed PD per RECIST 1.1 • ECOS PS 0 or 1 • Available tumour tissue sample obtained upon progression, if feasible • No exposure to systemic anti-cancer therapies post discontinuation of study chemotherapy • Completed follow-up visit 1 after discontinuation of study chemotherapy (approx. 30 days post last dose of study treatment)

Abbreviations: 1L, first line; AE, adverse event; AST/ALT, aspartate transaminase/alanine aminotransferase; BICR, blinded independent central review; CRR, complete response rate; CLCr, creatinine clearance; CTLA-4, cytotoxic T-lymphocyte antigen-4; DCR, disease control rate; dMMR, DNA mismatch repair deficiency; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IHC, immunohistochemistry; INR, international normalised ratio; IPI, ipilimumab; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low MSS, microsatellite stable; NIVO, nivolumab; OS, overall survival; PD, progressive disease; PD-1, programmed death 1; PD-L, programmed death ligand; PFS, progression-free survival; pMMR, proficient DNA mismatch repair; PCR, polymerase chain reaction; PRO, patient-reported outcomes; PTT, partial thromboplastin time; PT/INR, prothrombin time test/international normalised ratio; RECIST, response evaluation criteria in solid tumours; SAE, severe adverse event; TTR, time to response; ULN, upper limit of normal; WBC, white blood cells; WOCBP, women of childbearing potential

B.2.3.3 Study medications

Table 11 describes the study treatments and dosing schedules in CM8HW, with a list of prohibited concomitant medications.

Table 11. CM8HW study treatments

Study drugs	NIVO + IPI
	• NIVO 240mg as a 30 minute infusion + IPI 1mg/kg as a 30 minute infusion on day 1 of cycle 1 and then every 3 weeks thereafter for a total of 4 doses • Followed by NIVO 480mg every 4 weeks, for up to 2 years
	NIVO (results not reported in this submission)
	• NIVO 240mg as a 30 minute infusion on day 1 and then every 2 weeks for 6 doses, followed by NIVO 480mg every 4 weeks for up to 2 years
	mFOLFOX6
	• Oxaliplatin 85 mg/m^2, leucovorin 400 mg/^{2}, fluorouracil 400 mg/m^2 bolus, followed by fluorouracil 2400 mg/m^2 in continuous infusion over 46h on days 1, 15 and 29 during cycles 1 and 2 • Starting from cycle 3 day 1, the drugs will be administered on day 1 and day 15 of each subsequent cycle
	mFOLFOX6 + bevacizumab
	• Bevacizumab 5 mg/kg will be administered, followed by administration of mFOLFOX • Bevacizumab may be administered over a 90, 60 or 30 minute infusion, depending on tolerability
	mFOLFOX6 + cetuximab
	• Cetuximab 500 mg/m^2 will be administered, followed by administration of mFOLFOX • Cetuximab may be administered over a 2 hour or 1 hour infusion, depending on tolerability
	FOLFIRI
	• Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil bolus 400 mg/m^2 followed by fluorouracil 2400 mg/m^2 in continuous infusion over 46h on days 1, 15 and 29 during cycles 1 and 2 • Starting from cycle 3 day 1, the drugs will be administered on day 1 and day 15 of each subsequent cycle
	FOLFIRI + bevacizumab
	• Bevacizumab 5 mg/kg will be administered, followed by administration of FOLFIRI • Bevacizumab may be administered over a 90, 60 or 30 minute infusion, depending on tolerability
	FOLFIRI + cetuximab

	• Cetuximab 500 mg/m^2 will be administered, followed by administration of FOLFIRI • Cetuximab may be administered over a 2 hour or 1 hour infusion, depending on tolerability
Treatment duration	Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)
Prohibited prior and concomitant medications	• Treatment with immunosuppressive agents or immunosuppressive doses of systemic corticosteroids within 14 days of randomisation • Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA-4 antibody, or any other antibody drug targeting T-cell co-stimulation or immune checkpoint pathways • Participants who received cancer-related investigational products within 28 days or 5 half-lives, whichever is longer, prior to randomisation. Prior systemic anti-cancer treatment or palliative radiotherapy must have been completed at least 14 days prior to randomization. • Concurrent anti-neoplastic therapy • Botanical preparations intended to treat the disease under study • Any live or attenuated vaccine within 30 days of randomisation • Participants receiving irinotecan: non-topical medications known to be strong inducers or inhibitors of CP3A4, or strong inhibitors of UGT1A1 • Participants receiving bevacizumab: ongoing treatment with aspirin (>325mg per day) or other medication known to predispose patients to GI ulceration

Abbreviations: AE, adverse event; CTCAE, common terminology criteria for adverse events; CTLA-4, cytotoxic T-lymphocyte antigen-4; GI, gastrointestinal; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-1, programmed death 1; PD-L, programmed death ligand

B.2.3.4 Endpoints

The primary endpoint in CM8HW is PFS per blinded independent central review (BICR), and a key secondary endpoint is PFS per investigator (Table 12). The primary analysis population for PFS is patients with centrally-confirmed dMMR/MSI-H status, although PFS endpoints are also evaluated for all randomised patients, who were enrolled based on locally-confirmed dMMR/MSI-H status. Table 12 provides details of how primary, secondary and safety endpoints are defined and assessed.

Table 12. CM8HW summary of endpoints

	Endpoints	Primary analysis population	Definition	Assessment schedule
Primary efficacy endpoint(s)	PFS by BICR criteria	Confirmed dMMR/ MSI-H	Time from date of randomisation to date of first objectively documented disease progression per RECIST 1.1, or death due to any cause, whichever occurs first	Tumour assessment is conducted using CT and MRI of the chest, abdomen, pelvis, and all known sites of disease, and occurs: • At baseline • Until week 96: Every 6 weeks from treatment assignment for the first 24 weeks, and every 8 weeks thereafter, until either progression is confirmed or treatment is discontinued, whichever occurs later • Week 97 to week 144: every 16 weeks until progression is confirmed • Beyond week 144: every 24 weeks until progression is confirmed
Key secondary endpoint(s)	PFS by investigator	Confirmed dMMR/ MSI-H	Time from date of randomisation to date of first objectively documented disease progression per RECIST 1.1, or death due to any cause, whichever occurs first	
	PFS by BICR criteria	All randomised participants (dMMR/MSI-H confirmed by local testing)	Time from date of randomisation to date of first objectively documented disease progression per RECIST 1.1, or death due to any cause, whichever occurs first	
	ORR/DCR	Confirmed dMMR/ MSI-H	ORR is defined as the proportion of all randomised participants whose best overall response (BOR) is either confirmed CR or confirmed PR DCR is defined as the proportion of participants whose BOR is confirmed CR, confirmed PR or SD for at least 12 weeks The best overall response is defined as the best response designation, recorded between the randomisation date and the date of initial documented PD per RECIST v1.1, or the date of initiation of subsequent therapy, whichever occurs first.	

			For participants without documented progression or initiation of subsequent therapy, all available response designations will contribute to the BOR assessment	
Other secondary outcomes	TTR/DOR	Response evaluable	TTR is defined as the time from date of randomisation to date of first confirmed CR or PR DOR is defined as the time between date of first confirmed response (CR or PR) and the date of first documented PD or death due to any cause, whichever occurs first	
	OS	Confirmed dMMR/ MSI-H	Time from date of randomisation to the date of death due to any cause.	
Exploratory safety and QoL outcomes	Safety evaluation	Treated	Incidence of AEs and SAEs, AEs leading to discontinuation (with or without relationship to study drug), and deaths. Select AEs and IMAEs recorded separately AEs are recorded and graded according to CTCAE	AEs are recorded at each visit; information is collected for a minimum of 100 days following discontinuation of study treatment
	Patient-reported outcomes	Outcomes research population	EORTC QLQ-CR29, EORTC QLQ-CR30 and EQ-5D-3L questionnaires administered	Assessed prior to dosing in first three treatment cycles, and then every other cycle thereafter

Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CR, complete response; CT, computed tomography; CTCAE, common terminology criteria for adverse events; DCR, disease control rate; dMMR, DNA mismatch repair deficiency; DOR, duration of response; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-3L, EuroQol 5-dimensions 3-levels; IMAE, immune modulated adverse events; MRI, magnetic resonance imaging; MSI-H, microsatellite instability high; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QoL, quality of life; SAE, serious adverse event; TTR, time to response

In addition to standard reporting of AEs, AEs of special interest are selected based on the following rules:

1. AEs that may differ in type, frequency, or severity from AEs caused by non-IOs
2. AEs that may require immunosuppression as part of their management
3. AEs whose early recognition and management may mitigate severe toxicity
4. AEs for which multiple event terms may be used to describe a single type of AE

Further, immune-mediated AEs (IMAEs) are recorded, in order to characterise AEs of special clinical interest that may pertain specifically to treatment with IOs. IMAEs comprise specific events (or groups of MedDRA preferred terms [PTs] describing specific events) that include diarrhoea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, hypersensitivity/infusion reactions, and endocrine reactions.

Patients who discontinued study treatment are followed up for collection of survival data until death or the conclusion of the study, whichever comes first ('survival follow-up period'). In terms of safety, only AEs related to study drugs are recorded in this period.

Censoring rules

Censoring rules are applied for survival endpoints. For OS, patients who did not die are censored on their last known date alive. PFS censoring rules were as follows:

1. Patients who die without a reported prior progression and without initiation of subsequent anti-cancer therapy are considered to have progressed on the date of their death
2. Patients who did not progress or die are censored on the date of their last tumour assessment
3. Patients who did not have any on-study tumour assessments and did not die are censored at the randomisation date

4. Patients who received subsequent anti-cancer therapy or crossed over to receive treatment aligned to another arm of the trial are censored at the date of the last evaluable tumour assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy/crossover.

B.2.3.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.3.5.1 Randomisation

Patients who had not received prior therapy for mCRC were randomised to NIVO monotherapy, NIVO + IPI combination therapy, or chemotherapy in a 2:2:1 ratio.

B.2.3.5.2 Sample size and power

For the primary endpoint of PFS per BICR for NIVO + IPI vs. chemotherapy in the 1L population, it was determined that approximately 125 PFS events would provide ~99% power to detect an average HR of 0.55 with a two-sided alpha of 0.044. Therefore, approximately 230 1L subjects were required for randomisation in a 2:1 ratio to achieve this endpoint.

An interim analysis was planned for when approximately 85% (106 events) of the total number of events had been observed. The results of this interim analysis are presented.

B.2.3.5.3 Analysis populations

Table 13 describes analysis populations for primary and secondary endpoints.

The primary analysis population for the primary endpoint comprises those whose dMMR/MSI-H status has been centrally confirmed. Central testing protocols employ either an IHC panel that tested for the absence of MLH1, MSH2, MSH6 or PMS2 expression, or an MSI test that detected 7 novel biomarkers (ACVR2A, BTBD, DIDO1, MRE11, RYR3, SEC31A, and SULF2).[114]

Table 13. CM8HW analysis populations

Population	Description
Enrolled	All patients who signed an informed consent form and were registered into the IRT system
Randomised	All patients randomised to any arm
Confirmed dMMR/MSI-H	All randomised patients who have centrally confirmed dMMR/MSI-H status by central test per IHC or PCR
Treated	All patients who received at least one dose of study treatment
Response evaluable	All randomised patients who have baseline and at least one on-study evaluable tumour measurement. This population was defined based on Investigator and BICR data.
Outcomes research	All randomised patients who have an assessment at baseline and at least one subsequent post-baseline assessment (for EORTC QLQ-C30, QLQ-CR29 and EQ-5D-3L separately)
Crossover cohort	All randomised patients who received at least one dose of study treatment following crossover to the NIVO + IPI arm

Abbreviations: BICR, blinded independent central review; dMMR, DNA mismatch repair deficiency; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-3L, EuroQol 5-dimensions 3-levels; IHC, immunohistochemistry; IRT, interactive response technology; MSI-H, microsatellite instability high; PCR, polymerase chain reaction

B.2.3.5.4 Endpoints

Table 14 describes the statistical methods used for primary and secondary endpoints. In the crossover cohort, the same methodologies as used for the primary, secondary and exploratory efficacy endpoints are used where feasible.

Table 14. CM8HW summary of statistical methods

Endpoints	Statistical method
PFS (both BICR assessed and investigator assessed)	The distribution of PFS is compared via a two-sided, log-rank test at the allocated significance level at interim and at final analysis. In any case where the proportional hazards assumption does not hold, PFS is compared via a two-sided max-combo test. The HR and the corresponding 100x CI are estimated in a stratified Cox proportional hazards model using the randomised arm as a single covariate, stratified by line of therapy and tumour sidedness. PFS curves are estimated using the KM product-limit approach. Median PFS with two-sided 95% CIs are computed using the Brookmeyer and Crowley method with log-log transformation. In addition, PFS rates at a specific time points with two-sided 95% CI using the log-log transformation are computed.
OS/DOR	As per PFS
ORR/DCR	ORR is compared using a two-sided stratified Cochran Mantel Haenszel test. Associated ORs and an estimate of the difference in ORRs with 95% CI are calculated. Results for ORR/DCR are summarised by binomial response rates and corresponding two-sided 95% exact CIs, using the Clopper-Pearson method.
TTR	TTR is presented using summary statistics.
PROs	Baseline, on-treatment measurements, and change from baseline are summarised using descriptive statistics.
Safety evaluations	AEs are summarised using the worst CTC grade. Participants are only counted once at the PT level, once at the SOC level, and once in the 'Total participant' row at their worst CTC grade, regardless of SOC or PT. Deaths are summarised using frequency distribution.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CTC, common terminology criteria; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; KM, Kaplan-Meier; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient reported outcome; PT, preferred term; SOC, system organ class; TTR, time to response

B.2.3.6 Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence provided in this submission is derived from a large phase 3 trial conducted in line with the requirements of regulatory bodies. The complete quality assessment of CM8HW is summarised in Table 15. A quality assessment of the trials identified during the clinical SLR was conducted based on the Centre for Reviews and Dissemination's (CRD's) guidance and is provided in Appendix D. This was used to inform the indirect treatment comparison (ITC); additional detail is provided in Appendix E.

Table 15. Quality assessment results for CM8HW

	CM8HW
Was randomisation carried out appropriately?	Yes. In both enrolment periods, patients who had received no prior therapy were randomised to NIVO + IPI, NIVO or chemotherapy in a 2:2:1 ratio. All patients were stratified by tumour location (right vs. left) and by the number of prior treatments for metastatic disease (none, 1, ≥ 2). For NIVO + IPI vs. chemotherapy in the 1L setting, it was determined that 125 PFS events would provide 99% power to detect an HR of 0.55, requiring 230 patients to be randomised across both arms.
Was the concealment of treatment allocation adequate?	The study was open-label. This was deemed appropriate due to the differing safety profiles of the study treatments, thus allowing accurate assessment of the unique toxicities associated with each drug. In addition, the regimens being compared required different dosing schedules.
Were the groups similar at the onset of the study in terms of prognostic factors?	Yes, the baseline characteristics were generally balanced across arms (Table 17)
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, the study was open-label. This was deemed appropriate due to the differing safety profiles of the study treatments, thus allowing accurate assessment of the unique toxicities associated with each drug. In addition, the regimens being compared required different dosing schedules.
Were there any unexpected imbalances in dropouts between groups?	There was a larger proportion of discontinuations in the chemotherapy arm than in the NIVO + IPI arm; however, this is explained by a high number of dropouts due to disease progression, and is therefore, related to the differing efficacy of the drugs (Table 16).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Outcomes presented in this report are those considered relevant to the decision problem; all other outcomes are reported in the clinical study report
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, ITT analysis was conducted. In the ITT population (all randomised patients), ~15% were not confirmed dMMR/MSI-H by central testing. This population may therefore be less representative of the population addressed in the decision problem of this appraisal, containing some patients without dMMR/MSI-H tumours. However, since the central testing protocol aligns broadly with NHS guidance, the centrally-confirmed population is expected to align with the UK dMMR/MSI-H population. Missing dates were imputed as follows in the PFS analysis: progression dates were imputed as the first of the month if only the day was missing, and compared with the death date if present and complete. The earliest date was then taken as the date of progression. If the month or year was missing from the date of progression, or if the date was missing entirely, the value was not imputed and was treated as missing.
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[115]	

B.2.3.7 Clinical effectiveness results of the relevant studies

At the time of the interim analysis (clinical cutoff 12 October 2023), the information fraction was 80% (100 events occurred). In the randomised population, minimum follow-up time was 6.1 months, maximum was 48.4 months, and median was 31.5 months.[114,116] Due to data immaturity, OS and other secondary endpoints were not tested in the interim analysis presented here, as per the hierarchical testing strategy pre-defined in the trial protocol. These analyses will be available in future database locks (DBL).[117]

B.2.3.7.1 Baseline characteristics and patient disposition

Table 16 presents the patient disposition and flow in CM8HW. 303 patients with previously untreated dMMR/MSI-H mCRC were randomised (202 to NIVO + IPI and 101 to chemotherapy). Of these, 255 (84.2%) had centrally confirmed dMMR/MSI-H, with very similar proportions in the NIVO + IPI (171 [84.7%]) and chemotherapy arms (84 [83.2%]).[118]

In the chemotherapy arm (n=101), [redacted] patients crossed over from chemotherapy to NIVO + IPI as a result of disease progression. At the data cutoff date, [redacted] were receiving ongoing crossover treatment, [redacted] completed crossover treatment, and [redacted] discontinued crossover treatment with NIVO + IPI.

A further [redacted] patients in the chemotherapy arm received subsequent IO therapy after discontinuation of study treatment. Taken together with crossover patients and those receiving other systemic therapies, [redacted] ([redacted] of patients in the chemotherapy arm received subsequent systemic therapy. In the NIVO + IPI arm, [redacted] of patients received subsequent systemic therapy.[114]

In the treated population (excluding the crossover cohort), the median duration of NIVO + IPI therapy was 13.5 months (NIVO: 13.5 months, IPI: 2.1 months), whilst the median duration of chemotherapy was 4.0 months.[118] In the NVIO + IPI arm, 48.0% of patients discontinued treatment, with 19.0% doing so due to disease progression; in the chemotherapy arm, 93.2% discontinued, with 69.3% discontinuing due to progression.[114,118]

Of those treated in the chemotherapy arm (n = 88), 66 (75.0%) patients received targeted therapies, with 56 (63.6%) receiving bevacizumab and 10 (11.4%) receiving cetuximab.[118] [redacted] received oxaliplatin-containing regimens (mFOLFOX6), and [redacted] received irinotecan-containing regimens (FOLFIRI).[114]

Table 16. CM8HW patient disposition

N(%)	NIVO+ IPI (n = 202)	Chemotherapy (n = 101)	Total (n = 303)
Randomised	202	101	303
Randomised with centrally confirmed dMMR/MSI-H	171 (84.7)	84 (83.2)	255 (84.2)
Treated	200 (99.0)	88 (87.1)	288 (95.0)
Reason not treated			
Withdrew consent	[redacted]	[redacted]	[redacted]
No longer meets study criteria	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Ongoing treatment	42 (21.0)	6 (6.8)	48 (16.7)
Completed treatment	62 (31.0)	0 (0.0)	62 (21.5)
Discontinued treatment	96 (48.0)	82 (93.2)	178 (61.8)
Reason discontinued treatment			
Withdrew consent	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]
No longer meets study criteria	[redacted]	[redacted]	[redacted]
Disease progression	38 (19.0)	61 (69.3)	99 (34.4)
Unacceptable toxicity	36 (18.0)	4 (4.5)	40 (13.9)
AE unrelated to study drug	12 (6.0)	5 (5.7)	17 (5.9)
Maximum clinical benefit	0 (0.0)	8 (9.1)	8 (2.8)
Other	[redacted]	[redacted]	[redacted]
Discontinued due to C19	[redacted]	[redacted]	[redacted]
Ongoing study†	[redacted]	[redacted]	[redacted]
Discontinued study†	[redacted]	[redacted]	[redacted]
Reasons for discontinuation of study†			
Withdrew consent	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Loss to follow-up	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Discontinued due to C19†	[redacted]	[redacted]	[redacted]

†Includes data from crossover cohort

Abbreviations: AE, adverse event; C19, Coronavirus-19; dMMR, DNA mismatch repair deficiency; IPI, ipilimumab; MSI-H, microsatellite instability high; NIVO, nivolumab

Baseline characteristics were generally balanced between arms (Table 17). In the NIVO + IPI and chemotherapy arms, median age was 62.0 and 65.0 years respectively, median weight was [redacted] and [redacted], and the percentage male was 47% and 45%. In terms of region, [redacted] and [redacted] were in the US/Canada/Europe region respectively.[114,116,118]

Prognostic factors were also similar across groups. In the NIVO + IPI and chemotherapy arms, 42.1% and 48.5% of mCRC cases were diagnosed at stage IV respectively; 68.3% and 67.3% of tumours were right-sided; 37.6% and 41.6% of patients had liver metastases; 25.7% and 23.8% of tumours had BRAF mutation, 21.3% and 20.8% had KRAS/NRAS mutation and [redacted]% and [redacted]% of patients were ECOG PS ≥ 1.[114,116,118]

Table 17. CM8HW baseline characteristics

	NIVO+ IPI (n = 202)	Chemotherapy (n = 101)	Total (n = 303)
Age, years, median (min, max)	62.0 (21, 86)	65.0 (26, 87)	[redacted]
Age, categorical, n (%)			
Age < 65	117 (57.9)	46 (45.5)	163 (53.8)
Age ≥ 65	85 (42.1)	55 (54.5)	140 (46.2)
Age < 75	[redacted]	[redacted]	[redacted]
Age ≥ 75	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	95 (47.0)	45 (44.6)	140 (46.2)
Female	107 (53.0)	56 (55.4)	163 (53.8)
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black/African American	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Region, n (%)			
US/Canada/Europe	133 (65.8)	71 (70.3)	204 (67.3)
Asia	19 (9.4)	11 (10.9)	30 (9.9)
Other	50 (24.8)	19 (18.8)	69 (22.8)
ECOG PS, n (%)			

	NIVO+ IPI (n = 202)	Chemotherapy (n = 101)	Total (n = 303)
0	111 (55.0)	52 (51.5)	163 (53.8)
≥ 1	[redacted]	[redacted]	[redacted]
Weight, kg, median (min, max)	[redacted]	[redacted]	[redacted]
Stage at diagnosis, n (%)			
Stage II	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]
Stage IV	85 (42.1)	49 (48.5)	134 (44.2)
Not reported	[redacted]	[redacted]	[redacted]
Stage at study entry, n (%)			
Stage IVA	[redacted]	[redacted]	[redacted]
Stage IVB	[redacted]	[redacted]	[redacted]
Stage IVC	[redacted]	[redacted]	[redacted]
Histological grade, n (%)			
GX	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Cell type, n (%)			
Adenocarcinoma	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Tumour location, n (%)			
Cecum	[redacted]	[redacted]	[redacted]
Colon ascending/ hepatic flexure	[redacted]	[redacted]	[redacted]
Colon transverse	[redacted]	[redacted]	[redacted]
Colon descending/ splenic flexure	[redacted]	[redacted]	[redacted]
Colon sigmoid	[redacted]	[redacted]	[redacted]
Rectum/ rectosigmoid junction	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Tumour sidedness, n (%)			
Left	[redacted]	[redacted]	[redacted]
Right	138 (68.3)	68 (67.3)	206 (68.0)
Time from initial diagnosis to randomisation, n (%)			
< 1 year	[redacted]	[redacted]	[redacted]

	NIVO+ IPI (n = 202)	Chemotherapy (n = 101)	Total (n = 303)
≥ 1 year, < 3 years	[redacted]	[redacted]	[redacted]
≥ 3 years	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Liver metastasis per BICR, n (%)			
Yes	76 (37.6)	42 (41.6)	118 (38.9)
No	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Lung metastasis per BICR, n (%)			
Yes	44 (21.8)	25 (24.8)	69 (22.8)
No	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Peritoneal metastasis per BICR, n (%)			
Yes	84 (41.6)	43 (42.6)	127 (41.9)
No	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
PD-L1 status, n (%)			
≥1%	43 (21.3)	12 (11.9)	55 (18.2)
<1%	145 (71.8)	80 (79.2)	225 (74.3)
Not evaluable/ indeterminate	[redacted]	[redacted]	[redacted]
Not available	[redacted]	[redacted]	[redacted]
MSI-H and/or dMMR per central assessment, n (%)			
MSI-H and/or dMMR	171 (84.7)	84 (83.2)	255 (84.2)
MSS and pMMR	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
MMR per central assessment, n (%)			
dMMR	[redacted]	[redacted]	[redacted]
pMMR	[redacted]	[redacted]	[redacted]
Not available	[redacted]	[redacted]	[redacted]
MMR per local assessment, n (%)			
dMMR	[redacted]	[redacted]	[redacted]
pMMR	[redacted]	[redacted]	[redacted]
Not available	[redacted]	[redacted]	[redacted]
MSI per central assessment, n (%)			
MSI-H	[redacted]	[redacted]	[redacted]
MSS	[redacted]	[redacted]	[redacted]
Not available	[redacted]	[redacted]	[redacted]
MSI per local assessment, n (%)			

	NIVO+ IPI (n = 202)	Chemotherapy (n = 101)	Total (n = 303)
MSI-H	[redacted]	[redacted]	[redacted]
MSS	[redacted]	[redacted]	[redacted]
Not available	[redacted]	[redacted]	[redacted]
BRAF/KRAS/NRAS mutation status, n (%)			
BRAF/KRAS/NRAS all WT	47 (23.3)	23 (22.8)	70 (23.1)
BRAF mutant	52 (25.7)	24 (23.8)	76 (25.1)
KRAS/NRAS mutant	43 (21.3)	21 (20.8)	64 (21.1)
BRAF and KRAS/NRAS mutant	[redacted]	[redacted]	[redacted]
Unknown	55 (27.2)	31 (30.7)	86 (28.4)
Lynch syndrome, n (%)			
Yes	22 (10.9)	17 (16.8)	39 (12.9)
No	135 (66.8)	49 (48.5)	184 (60.7)
Unknown	44 (21.8)	30 (29.7)	74 (24.4)
Not reported	[redacted]	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; dMMR, DNA mismatch repair deficiency; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GX, grade cannot be assessed; IPI, ipilimumab; MMR, DNA mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatellite stable; NIVO, nivolumab; PD-L1, programmed death ligand 1; pMMR, DNA mismatch repair proficiency

B.2.3.7.2 Key efficacy results: PFS

All clinical effectiveness results shown for CM8HW are from the interim analysis (cutoff date 12 October 2023), as the number of events required for the final analysis have not been reached. The results presented include the primary endpoint, PFS per BICR for NIVO + IPI vs. chemo in the 1L population in those with centrally confirmed dMMR/MSI-H status. In addition, this submission presents the key secondary endpoints, PFS per BICR in all randomised patients, and PFS per investigator in the centrally confirmed population.

It should be noted that a high proportion of patients in the chemotherapy arm received bevacizumab 56 (63.6% treated patients).[118] As bevacizumab is not reimbursed for use in UK clinical practice in this indication, subgroup analyses have been conducted which exclude patients who received bevacizumab. Subgroup analyses are presented in Section B.2.5.1.

Minimum follow-up (to clinical cutoff date) in all randomised patients was 6.1 months, and median follow-up was 31.6 months. At data cutoff, 100 events had occurred, leading to an information fraction of 80%.[114,116]

B.2.3.7.2.1 PFS per BICR in all randomised patients

In previously untreated patients with dMMR/MSI-H mCRC, NIVO + IPI demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR compared with chemotherapy, in all randomised patients. Median PFS was not reached after [redacted] months of follow-up in the NIVO + IPI arm, whereas the chemotherapy arm had a median PFS of [redacted] months; the HR was in favour of NIVO + IPI [redacted] (95% confidence interval [CI] [redacted]) (Table 18).[114,116]

Moreover, the Kaplan-Meier (KM) curves show pronounced and sustained separation after three months post-randomisation (Figure 7).

Table 18. CM8HW PFS results for all randomised subjects (interim analysis)

	NIVO + IPI (n = 202)	Chemotherapy (n = 101)
PFS per BICR		
Events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)	0.32 (0.23, 0.46)	
PFS rates, % (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; PFS, progression-free survival; NA, not available; NIVO, nivolumab; NR, not reached

Figure 7. CM8HW KM curves for PFS per BICR in all randomised subjects (interim analysis)

Abbreviations: BICR, blinded independent central review; CI, confidence interval; IPI, ipilimumab; NA, not available; NIVO, nivolumab; PFS, progression-free survival

B.2.3.7.2.2 PFS in centrally confirmed population

In previously untreated patients with centrally confirmed dMMR/MSI-H mCRC, NIVO + IPI demonstrated a statistically significant and clinically meaningful improvement in PFS per BICR compared with chemotherapy, meaning the primary endpoint was met. Median PFS was not reached after 31.6 months of follow-up in the NIVO + IPI arm, whereas the chemotherapy arm had a median PFS of 5.9 (4.4, 7.9) months (Table 19). The HR was significantly in favour of NIVO + IPI (p<0.0001), both via the Cox model (0.21 [95% CI: 0.14, 0.32]) and via the max-combo test (. Results were similar for the key secondary endpoint, PFS per investigator; median PFS was in the NIVO + IPI group, but was in the chemotherapy group, with the HR strongly in favour of NIVO + IPI ([114,116,118] Visually, the PFS curves for the primary endpoint

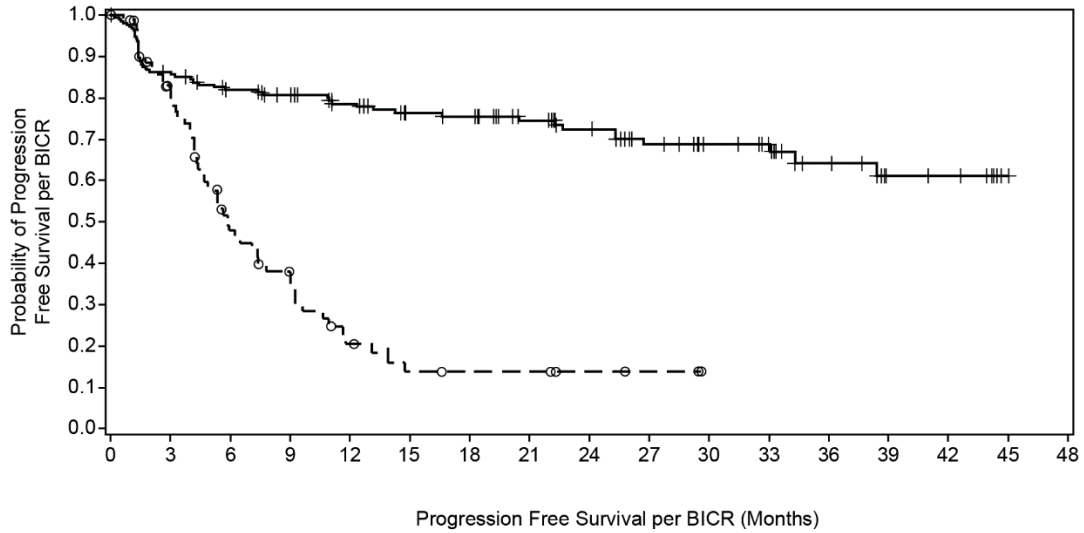
demonstrate pronounced separation, with a high initial plateau in the NIVO + IPI arm (PFS rate of ~80% at 12 months) leading to clear long-term benefit.[118]

Table 19. CM8HW PFS results for centrally confirmed population (interim analysis)

	NIVO + IPI (n = 171)	Chemotherapy (n = 84)
PFS per BICR		
Events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	NR (38.4, NA)	5.9 (4.4, 7.9)
HR (95% CI)		0.21 (0.14, 0.32)
p-value		p < 0.0001
HR by max-combo (95% CI)		[redacted]
p-value		[redacted]
PFS rates (95% CI)		
6 months	[redacted]	[redacted]
12 months	78.7[redacted]	20.6[redacted]
PFS per investigator		
Events, n (%)	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]
HR (95% CI)		[redacted]
PFS rates (95% CI)		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; PFS, progression-free survival; NA, not available; NIVO, nivolumab; NR, not reached

Figure 8. CM8HW KM curves for PFS per BICR in the centrally confirmed population (interim analysis)



Number of Subjects at Risk

Arm B: Nivo + Ipi	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Arm C: Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

Arm B: Nivo + Ipi (events : 48/171), median and 95% CI : N.A (38.44, N.A)

Arm C: Chemo (events : 52/84), median and 95% CI : 5.85 (4.37, 7.79)

Arm B: Nivo + Ipi vs. Arm C: Chemo - hazard ratio (95% CI) : 0.21 (0.14, 0.32)

Arm B: Nivo + Ipi vs. Arm C: Chemo - hazard ratio (97.91% CI) : 0.21 (0.13, 0.35)

p-value: <0.0001

Abbreviations: BICR, blinded independent central review; CI, confidence interval; IPI, ipilimumab; NA, not available; NIVO, nivolumab; PFS, progression-free survival

Figure 9. CM8HW KM curves for PFS per investigator in the centrally confirmed population (interim analysis)

Abbreviations: CI, confidence interval; IPI, ipilimumab; NA, not available; NIVO, nivolumab; PFS, progression-free survival

B.2.3.7.3 Patient-reported outcomes: EQ-5D-3L scores

Completion rates for the EQ-5D-3L at baseline were [redacted] for subjects in the NIVO + IPI, arm and [redacted] in the chemotherapy arm. At follow-up visits 1 and 2, completion rates were [redacted] and [redacted] in the NIVO + IPI arm and [redacted] and [redacted] in the chemotherapy arm.[114]

Mean EQ-5D-3L utility scores were the same across both arms for all randomised participants at baseline ([redacted] for both). In the NIVO + IPI arm, there was a trend towards improvement of the EQ-5D-3L utility scores with a sustained improvement from baseline over the study; at several timepoints during follow-up to Week 101, the mean change from baseline reached the minimal clinically important difference (MCID) of +0.08 (Figure 10).[119] In the chemotherapy arm, whilst declining

number of responders over time lead to large confidence intervals, there was a trend towards worsening utility scores and a clear separation from the NIVO + IPI arm.

Figure 10. CM8HW: mean Changes in EQ-5D-3L Utility Index Score from baseline in all randomised subjects (interim analysis)

Abbreviations: EQ-5D-3L, EuroQol 5-demensional questionnaire (3 levels); IPI, ipilimumab; NA, not available; NIVO, nivolumab

B.2.4 CheckMate 142

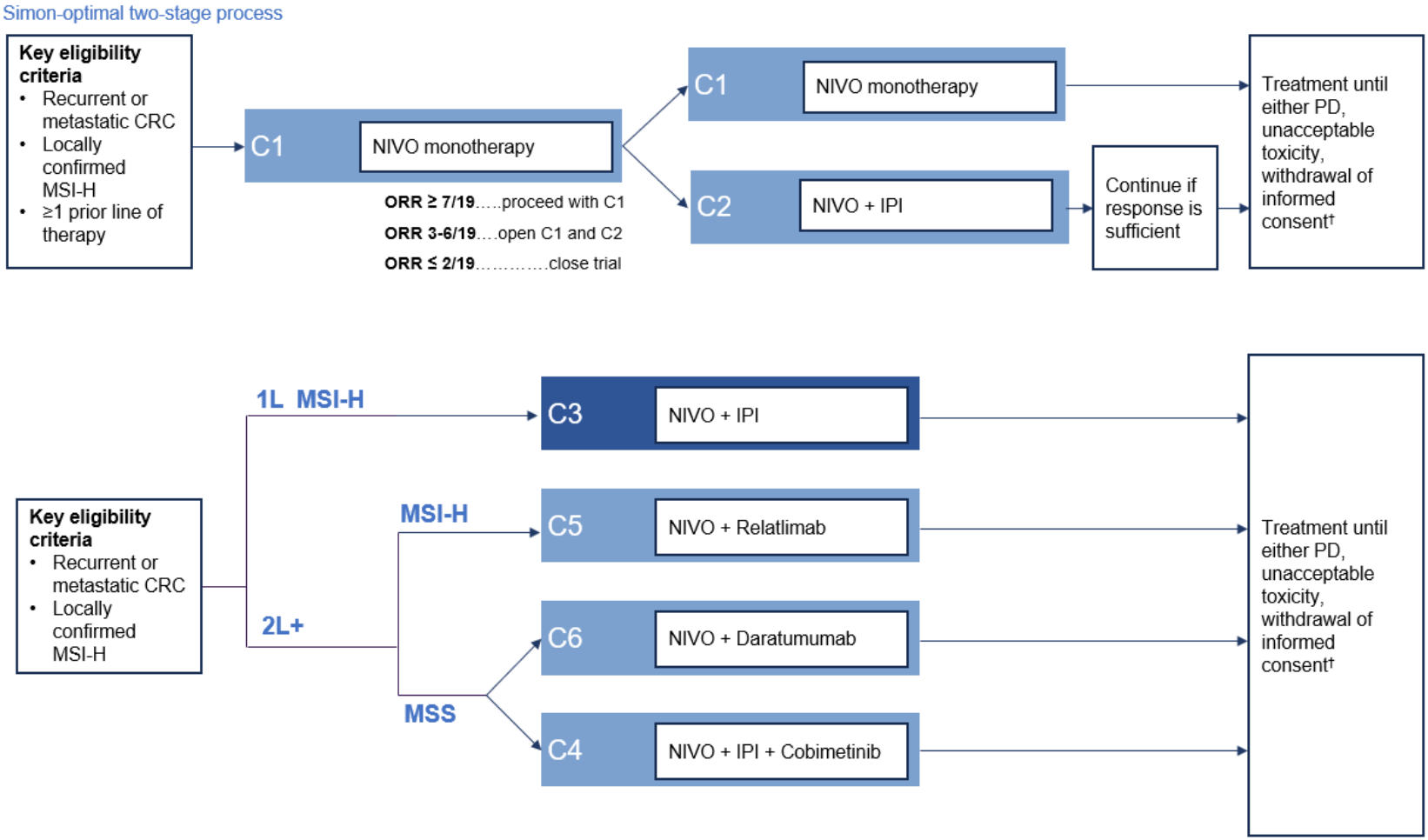
B.2.4.1 Summary of methodology

CM142 was a phase 2, non-randomised, open-label, multicentre trial investigating the efficacy and safety of NIVO, either as monotherapy or in combination with IPI or other agents. Data from CM142 are presented as supporting evidence, as CM8HW is ongoing and survival data have not yet reached maturity, particularly in the NIVO + IPI arm. Response and survival data collected during a median of 64.2 months of follow-up in 1L MSI-H mCRC patients treated with NIVO + IPI are presented here.

The study consisted of 6 cohorts (Figure 11); Cohorts 1 and 2 formed part of a two-stage process, in which 19 patients with previously-treated MSI-H were initially recruited to receive NIVO monotherapy. As fewer than 7 but more than 2 patients responded, additional patients were added to Cohort 1, and Cohort 2 (NIVO + IPI combination therapy) was initiated. The trial also included Cohort 3 (previously-untreated MSI-H mCRC), Cohorts 4 and 6 (previously-treated MSS mCRC), and Cohort 5 (previously-treated MSI-H mCRC).

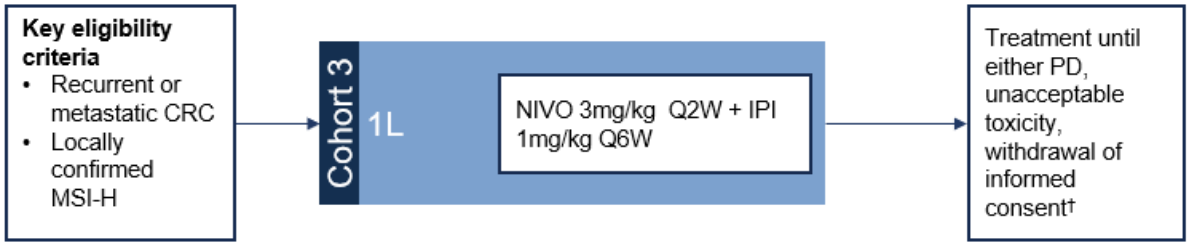
In this submission, the results of Cohort 3 are presented, which comprised people with previously-untreated mCRC of locally confirmed MSI-H status (Figure 12). Patients in Cohort 3 who discontinue treatment at maximum clinical benefit were eligible to re-initiate treatment if disease progression occurred within one year. Inclusion/exclusion criteria are presented in Table 20.[120]

Figure 11. Study design of CM142, including the 6 study cohorts



Abbreviations: 1L, first-line; 2L, second-line; CRC, colorectal cancer; IPI, ipilimumab; MSI-H, microsatellite instability high; MSS, microsatellite stable; NIVO, nivolumab; ORR, overall response rate; PD, progressive disease

Figure 12. CM142 study design



Abbreviations: 1L, first-line; CRC, colorectal cancer; IPI, ipilimumab; MSI-H, microsatellite instability high; NIVO, nivolumab; PD, progressive disease; Q2/6W, every 2/6 weeks

B.2.4.2 Inclusion/exclusion criteria

Table 20. CM142 Cohort 3 eligibility criteria

Eligibility criteria	• Signed written informed consent form • Histologically confirmed recurrent or metastatic CRC with no prior treatment for metastatic disease • Tumour MSI-H status confirmed by accredited laboratory per local practice • Measurable disease by CT/MRI per RECIST v1.1 • Participants with lesion in a previously irradiation field as the sole site of measurable disease are permitted to enrol provided the lesion(s) have demonstrated clear progression and can be measured accurately • Willing to provide tumour tissue (archival or fresh biopsy sample) • ECOG PS 0 or 1 • Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug administration • Subject may have refused chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. In this case, the subject's refusal must be thoroughly documented, and the investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility • Laboratory test findings: WBC ≥ 2000/uL; neutrophils ≥ 1500/uL; platelets ≥ 100 x 10^3/uL; haemoglobin > 9.0 g/dL; serum creatinine ≤ 1.5 x ULN unless CLCr ≥ 40 mL/min; AST/ALT ≤ 3.0 x ULN; bilirubin ≤ 1.5 x ULN, except participants with Gilbert syndrome • Aged ≥ 18 years • Women of childbearing potential must have negative pregnancy test and not be breastfeeding • Women of childbearing potential who are heterosexually active receiving nivolumab with or without ipilimumab must agree to follow instructions regarding contraception for the

	duration of treatment with study drugs plus at least 5 months after final dose • Males who are sexually active with women of childbearing potential and who are assigned to receive chemotherapy must agree to follow instructions regarding contraception for the duration of treatment with study drugs and for at least 7 months after final dose. Azoospermic males are exempt from contraceptive requirements
Exclusion criteria	See CSR for full details[120]
Re-initiation criteria	• PD per RECIST v1.1 within 52 weeks of treatment termination • Investigator-assessed clinical benefit • No rapid disease progression • Tolerance of study drug • Stable performance status • Adequate blood, liver, kidney and cardiac function as assessed in laboratory tests for inclusion • Adequate screening requirements met • Re-initiation will not delay intervention to prevent serious complications of progression • Written consent form

Abbreviations: 1L, first line; AE, adverse event; AST/ALT, aspartate transaminase/alanine aminotransferase; CT, computed tomography; CLCr, creatinine clearance; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; INR, international normalised ratio IPI, ipilimumab; MRI, magnetic resonance imaging; MSI-H, microsatellite instability high; NCI, National Cancer Institute; NIVO, nivolumab; PD, progressive disease; PTT, partial thromboplastin time; PTT/INR, prothrombin time test/international normalised ratio; RECIST, response evaluation criteria in solid tumours; ULN, upper limit of normal; WBC, white blood cells

B.2.4.3 Study medications

Table 21 presents the study medications in Cohort 3 of CM142, along with a list of prohibited concomitant medications.[120,121]

Table 21. CM142 Cohort 3 study treatments

Study drugs	NIVO + IPI
	• NIVO 3mg/kg + IPI 1mg/kg administered together on day 1 of cycle 1 and then once every 2 weeks (NIVO) or once every 6 weeks (IPI)
Treatment duration	Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or maximum clinical benefit However, subjects may be permitted to continue treatment for up to 2 years beyond initial investigator-assessed PD, if they meet the following requirements: • Investigator-assessed clinical benefit • No rapid disease progression • Tolerance of study drug • Stable ECOG PS • Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases) • Subject provides written informed consent prior to receiving any additional treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options
Prohibited prior and concomitant medications	• Immunosuppressive agents (except to treat a drug-related AE) • Systemic corticosteroids > 10 mg daily prednisone equivalent (except to treat a drug-related adverse event; additionally, a short course [<3 weeks] for prophylaxis of treatment if non-autoimmune conditions is permitted). • Live/attenuated vaccines (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and measles, • mumps, rubella) • Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, IOs, radiation therapy except for palliative radiation therapy [details in protocol] or standard or investigational agents for treatment of cancer). • Prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA-4 antibody, or any other antibody drug targeting T-cell co-stimulation or immune checkpoint pathways • Prior treatment with daratumumab or other anti-CD-28 therapies
Additional considerations	N/A

Abbreviations: AE, adverse event; CD-28, cluster of differentiation 28; CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; ICF, informed consent form; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; PD-1, programmed death 1; PD-L, programmed death ligand

B.2.4.4 Endpoints

The primary endpoint in CM142 was tumour response, as described by ORR, best overall response (BOR), duration of response (DOR) and complete response rate (CRR), and assessed per investigator. Key secondary endpoints included ORR, BOR, DOR and CRR per BICR, and DCR per investigator; exploratory endpoints included PFS and OS, per BICR and per investigator (Table 22). In the re-initiation population, primary, secondary and exploratory efficacy endpoints have the same definition, starting from the re-initiation start date as opposed to the date of first dose with study.[120,121]

Table 22. CM142 Cohort 3 summary of endpoints

	Endpoints	Primary Analysis Population	Definition	Assessment schedule
Primary efficacy endpoint(s)	ORR/BOR/ DOR/CRR by investigator	Response evaluable	BOR is defined as the best response recorded between the date of first dose of study drug and the date of initial PD per RECIST v1.1, or the date of subsequent therapy, whichever occurred first. For subjects without PD or subsequent therapy, all available response designations contributed to BOR. ORR is defined as the number of subjects with a BOR of CR or PR, divided by the number of treated subjects. CRR is defined as the number of subjects with a BOR of CR, divided by the number of treated subjects DOR is defined as the time from first confirmed response (CR or PR) to the date of first documented PD	Tumour assessment is conducted using CT and/or MRI of the chest, abdomen, pelvis, and all known sites of disease, and occurs: • At baseline • At 6 weeks from first dose • Until week 24: every 6 weeks • After week 24: every 12 weeks
Key secondary endpoint(s)	ORR/BOR/ DOR/CRR by BICR			
	DCR by investigator		DCR is defined as the number of participants with a BOR or CR, PR or SD lasting at least 12 weeks, divided by the number of treated subjects	
Key exploratory endpoint(s)	PFS, OS by investigator or by BICR	Treated	PFS is defined as the time from first dosing date to the date of first documented progression, as determined by investigator/BICR, or death from any cause, whichever occurred first	

			OS is defined as the time from first dosing date to the date of death	
Exploratory safety and QoL endpoints	Rate of Deaths, AEs, SAEs, AEs leading to discontinuation	Treated	The incidence of AEs, SAEs, AEs leading to discontinuation, AEs of special interest were graded using the NCI CTCAE version 4.0	AEs were reported by investigators, and were counted as on-treatment if the event occurred within 30 days of the last dose of study treatment, or 100 days for analyses specified as extended-follow-up
	Patient-reported outcomes	Outcomes research	EORTC QLQ-C30 and EQ-5D-3L questionnaires were administered	Questionnaires were completed before first dose of study drug, and every 6 weeks thereafter

Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CR, complete response; CRR, complete response rate; CT, computed tomography; CTCAE, common terminology criteria for adverse events; DCR, disease control rate; DOR, duration of response; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-3L, EuroQol 5-dimensions 3-levels; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QoL, quality of life; SAE, serious adverse event; SD, stable disease

Censoring rules

Censoring rules were applied for survival endpoints. For OS, patients who did not die were censored at their last known date alive. The PFS censoring rules were as follows:

1. Patients who did not progress or died were censored on the date of their last evaluable tumour assessment

2. Patients who did not have baseline on-study tumour assessments and did not die were censored on the first dosing date

3. Patients who initiated any subsequent anti-cancer therapy without prior recorded progression were censored at last evaluable tumour assessment prior to initiation of subsequent therapy

For DOR, patients who did not progress or died were censored on the date of their last evaluable tumour assessment.

B.2.4.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.5.1 Sample size and power

Sample size determination was based on the ability to estimate ORR with sufficient precision, rather than on power calculations. For a sample size of 30 patients, an ORR range of 45%–65% was considered to provide meaningful clinical outcome as compared to available data. Sample size was increased to 45 to ensure that at least 30 patients were confirmed as MSI-H per central testing.

B.2.4.5.2 Analysis populations

Table 23 describes analysis populations for primary, secondary and key exploratory endpoints in CM142.[120,121]

Table 23. CM142 Cohort 3 analysis populations

Population	Description
MSI-H	Patients defined as MSI-H based on standard diagnostic testing, including those confirmed in the current study using PCR

Population	Description
Treated	All patients who received at least one dose of study medication
Response evaluable	All patients who have evaluable tumour measurement at baseline, plus at least one on-study evaluable measurement
Outcomes research	All treated patients who have an assessment at baseline, plus at least one subsequent assessment, for either of the EORTC QLQ-C30 or EQ-5D questionnaires
Re-initiation	All patients who received at least one dose of study drugs following treatment re-initiation

Abbreviations: EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-3L, EuroQol 5-dimensions 3-levels; MSI-H, microsatellite instability high; PCR, polymerase chain reaction

B.2.4.5.3 Endpoints

Table 24 describes the statistical methods used for primary, secondary and key exploratory endpoints.[120,121]

Table 24. CM142 Cohort 3 summary of statistical methods

Endpoints	Statistical method
ORR/DOR/ DCR/CRR by investigator or by BICR	Estimates of ORR/CRR and corresponding 95% exact CIs were computed using the Clopper-Pearson method. DOR was summarised using the KM product-limit method. Median values, along with two-sided 95% CIs based on log-log transformation, were also calculated.
PFS by investigator or by BICR	PFS and OS were summarised descriptively using the KM product-limit method. Median values, along with two-sided 95% CIs based on log-log transformation, were also calculated. KM curves for PFS and OS were generated; PFS and OS rates at specific timepoints were estimated using KM estimates and associated two-sided 95% CIs were calculated.
PROs	Baseline, on-treatment measurements, and change from baseline were summarised using descriptive statistics, and proportion of patients demonstrating clinically meaningful deterioration were presented.
Safety evaluation	Descriptive safety statistics were presented using NCI CTCAE v 4.0. All on-study AEs, drug-related AEs, SAEs, and drug-related SAEs were tabulated by system organ class and MedDRA preferred term, using the worst CTC grade. On-study lab parameters including haematology, chemistry, liver function, thyroid function, and renal function were also summarised according to worst CTC grade.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CRR, complete response rate; CTCAE, common terminology criteria for adverse events; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; MeDRA, medical dictionary of regulatory activities; NCI, national cancer institute; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event

B.2.4.5.4 *Post-hoc* analysis: association between PFS and OS

Correlation was analysed in the 1L NIVO + IPI treated cohort. Copula functions (Clayton, Frank, Hougaard, Joe, and Plackett) were used to model PFS-OS dependence, and PFS and OS curves were represented by commonly-used parametric distributions. Joint PFS-OS models were evaluated based on statistical goodness-of-fit criteria, visual fit to KM curves, and clinical plausibility of survival extrapolations beyond the follow-up period. Correlation strength was measured by Spearman's rho. Results and interpretation of this analyses are discussed in Section B.2.4.7.2.2.1 and B.2.10.1.

B.2.4.6 Critical appraisal of the relevant clinical effectiveness evidence

The clinical effectiveness evidence derived from CM142 are conducted in line with the requirements of regulatory bodies. The quality assessment of CM142 is summarised in Table 25.

Table 25. Quality assessment results for CM142

	CM142
Was randomisation carried out appropriately?	No randomisation was carried out as this was a Phase II trial designed in part to inform a randomised Phase III trial.
Was the concealment of treatment allocation adequate?	The study was open-label, as there was no comparator arm.
Were the groups similar at the onset of the study in terms of prognostic factors?	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation?	The study was open-label, as there was no comparator arm.
Were there any unexpected imbalances in dropouts between groups?	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Outcomes presented in this report are those considered relevant to the decision problem; all other outcomes are reported in the clinical study report
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Primary analysis was conducted in the treated population. Additional analysis populations included all enrolled patients, all BICR and investigator response evaluable patients, immunogenicity patients, PD-L1 evaluable patients, biomarker patients and outcomes research patients.
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)[115]	

B.2.4.7 Clinical effectiveness results

B.2.4.7.1 Baseline characteristics and patient disposition

In Cohort 3 of CM142 (1L, MSI-H patients), 59 patients were enrolled, of whom 45 were treated; the most common reason for not being treated was not meeting study criteria (15.3%).

For pre-specified analyses, the median follow-up was 64.2 months (range 59.4 to 68.9); the median duration of NIVO treatment was 19.1 months, and for IPI treatment, this was 18.1 months. At end of follow-up, all treated patients had discontinued treatment, with the most common reason being that maximum clinical benefit was achieved (Table 26).[121]

Table 26. CM142 Cohort 3 patient disposition[120,121]

N (%)	NIVO+ IPI (n = 59)
Enrolled	[redacted]
Treated	[redacted]
Not treated	[redacted]
Reason not treated	
Withdrew consent	[redacted]
No longer meets study criteria	[redacted]
Adverse event	[redacted]
Other	[redacted]
	NIVO + IPI treated population (n = 45)
Ongoing treatment	0 (0.0)
Completed treatment	0 (0.0)
Discontinued treatment	45 (100)
Reason discontinued treatment	
Disease progression	8 (18)
AE related to treatment	7 (16)
AE unrelated to study drug	6 (13)
Patient request to discontinue	4 (9)
Loss to follow-up	1 (2)
Maximum clinical benefit	19 (42)

Abbreviations: AE, adverse event; IPI, ipilimumab; NIVO, nivolumab

The baseline characteristics of treated participants in Cohort 3 of CM142 (n=45) were similar to those of the NIVO + IPI cohort in CM8HW (n=202) (Table 27). The median age in CM142 was 66.0 years (62.0 years in CM8HW), with 51.1% male (53.0% in CM8HW). In CM142, the majority of patients [redacted] came from the European region, with [redacted] coming from the US (Table 27).[104,116,120]

The most common tumour location in CM142 was right-sided colon (57.8%); in the NIVO + IPI cohort of CM8HW, the most common tumour location was ascending colon/hepatic flexure ([redacted] which is on the right side of the colon, excluding the cecum. Additionally, in CM142 and CM8HW respectively, 37.8% and 25.7% of participants were positive for BRAF mutation.

Table 27. CM142 Cohort 3 baseline characteristics (treated)

	CM142 NIVO + IPI (Treated; N = 45)	CM8HW NIVO + IPI (Randomised; N = 202)
Age, years, median (min, max)	66.0 (21, 85)	62.0 (21, 86)
Age, categorical, n (%)		
Age < 65	22 (48.9)	117 (57.9)
Age ≥ 65	23 (51.1)	85 (42.1)
Sex, n (%)		
Female	22 (48.9)	95 (47.0)
Male	23 (51.1)	107 (53.0)
Race, n (%)		
White	43 (95.6)	[redacted]
Black/African American	1 (2.2)	[redacted]
Asian	1 (2.2)	[redacted]
Other	0 (0.0)	[redacted]
Weight, kg, mean (SD)	[redacted]	–
Weight, kg, median (min, max)	[redacted]	[redacted]
ECOG PS, n (%)		
0	25 (55.6)	111 (55.0)
1	20 (44.4)	[redacted]
Region, n (%)		
Europe	[redacted]	–
Australia	[redacted]	–
US	[redacted]	–
US/Canada/Europe	–	133 (65.8)
Asia	–	19 (9.4)
Other	–	50 (24.8)
Stage at diagnosis, n (%)		
Stage I	[redacted]	–
Stage II	[redacted]	[redacted]
Stage III	[redacted]	[redacted]
Stage IV	17 (37.8)	85 (42.1)
Not reported	–	[redacted]
Tumour location, n (%)		
Rectum	3 (6.7)	–
Left colon	4 (8.9)	–
Right colon	26 (57.8)	–
Transverse colon	3 (6.7)	[redacted]

Colon NOS	1 (2.2)	–
Colon sigmoid	8 (17.8)	[redacted]
Cecum	–	[redacted]
Colon ascending/ hepatic flexure	–	[redacted]
Colon descending/ splenic flexure	–	[redacted]
Rectum/ rectosigmoid junction	–	[redacted]
Unknown	–	[redacted]
Local MSI result, n (%)		
MSI-H	[redacted]	[redacted]†
MSS	–	[redacted]
Not reported	–	[redacted]
Other	[redacted]	–
Central MSI result, n (%)		
MSI-H	[redacted]	[redacted]‡
MSI-H/MSI-S	[redacted]	–
MSI-L	[redacted]	–
MSI-S	[redacted]	[redacted]
MSI-L/MSI-S	[redacted]	–
Not reported	[redacted]	[redacted]
BRAF/KRAS mutation status, n (%)		
KRAS/BRAF WT	13 (28.9)	
KRAS/NRAS/BRAF WT		47 (23.3)
BRAF mutation	17 (37.8)	52 (25.7)
KRAS mutation	10 (22.2)	–
KRAS/NRAS mutation	–	43 (21.3)
BRAF and KRAS/NRAS mutant	–	[redacted]
Unknown	5 (11.1)	55 (27.2)
Lynch syndrome, n (%)		
Yes	[redacted]	22 (10.9)
No	[redacted]	135 (66.8)
Unknown	[redacted]	44 (21.8)
Not reported	–	[redacted]

†As per enrolment criteria, all patients included in CM8HW were required to have locally confirmed dMMR or MSI-H; a positive result for both tests was not considered necessary. Hence, those classed here as MSS or 'not reported' will have had locally confirmed dMMR.

‡In the overall CM8HW population, the rate of centrally confirmed dMMR/MSI-H was 84.7%. Therefore, some of those without centrally confirmed MSI-H will have centrally confirmed dMMR

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low; MSS, microsatellite stable; NIVO, nivolumab; NOS, not otherwise specified; SD, standard deviation

B.2.4.7.2 Key efficacy results

B.2.4.7.2.1 Investigator-assessed response, disease control and durability

In participants with previously untreated MSI-H mCRC, NIVO + IPI was associated with strong, durable response (Table 28). Investigator-assessed DCR and ORR were 84% and 71%, with 20% of participants achieving a complete response (CR). Time to response (TTR) was 2.7 months, and median DOR was not reached at 64.2 months of follow-up, with a median of 72% of participants still in response at 60 months. Hence, NIVO + IPI demonstrates durability of response in the MSI-H population.[121]

Table 28. CM142 response rates and response durability[121]CR

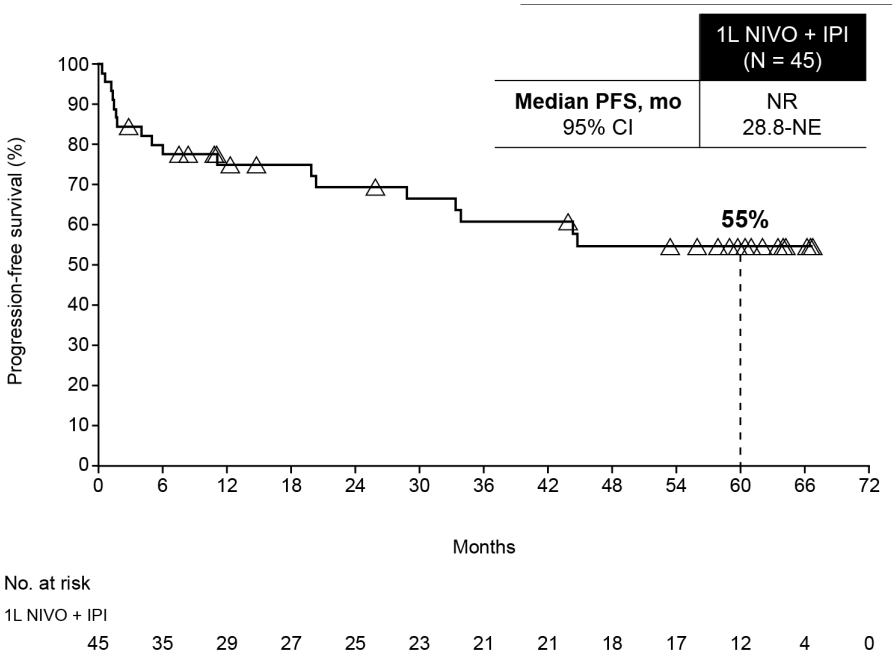
	NIVO+ IPI (n = 45)	95% CI
ORR, n (%)	32 (71)	(56–84)
BOR, n (%)		
CR	9 (20)	
PR	23 (51)	
SD	6 (13)	
PD	7 (16)	
DCR, n (%)	38 (84)	(71–94)
TTR, months, median (range)	2.7 (1.2–27.7)	
DOR, months, median	NR (42–NA)	
Rate evaluated at 60 months, %	72	(50–86)

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; IPI, ipilimumab; NIVO, nivolumab; ORR, overall response rate; TTR, time to response

B.2.4.7.2.2 PFS and OS

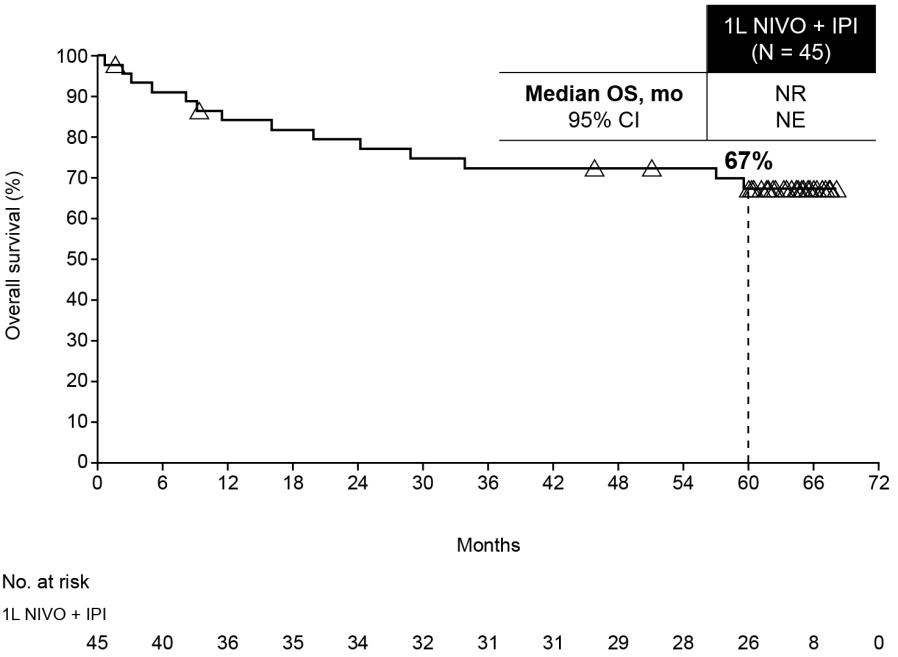
In participants with previously untreated MSI-H mCRC, NIVO + IPI was associated with long-term survival. Neither median PFS nor median OS were reached at 64.2 months of follow-up; at 60 months, PFS and OS rates were 55% and 67%, respectively (Figure 13, Figure 14).[121] Results of this analysis demonstrate that PFS benefits associated with NIVO + IPI may be reasonably expected to translate into long-term OS benefits; this is further explored in B.2.10.2.

Figure 13. CM142 KM curve for PFS[121]



Abbreviations: CI, confidence interval; IPI, ipilimumab; NE, not evaluable; NIVO, nivolumab; NR, not reached; PFS, progression-free survival

Figure 14. CM142 KM curve for OS[121]



Abbreviations: CI, confidence interval; IPI, ipilimumab; NE, not evaluable; NIVO, nivolumab; NR, not reached; OS, overall survival

B.2.4.7.2.2.1 Post-hoc analysis: PFS-OS correlation

Spearman's rho is a measure of rank correlation, which measures the degree to which two variables are monotonic functions of each other. A value of 1.0 denotes perfect rank association.[122]

The patient-level correlation between PFS and OS was analysed in the NIVO+IPI treated cohort (n=45, median follow-up 52.6 months). The range of estimates for Spearman's rho was 0.82–0.95; the estimate from the selected copula model was 0.92 (95% CI: 0.78, 0.98). This indicates that patient-level correlation between PFS and OS is strong, supporting the evidence for the validation of PFS as a suitable surrogate endpoint for OS in patients with MSI-H/dMMR mCRC.[123]

Additionally, across CM142 cohort 1 (2L+ NIVO monotherapy) and cohort 2 (2L+ NIVO + IPI), NIVO + IPI demonstrated (improvements over NIVO monotherapy in in observed improvements in ORR (39% vs. 65%), 5-year PFS (34% vs. 52%) and 5-year OS (46% vs. 68%),[84] using a similar IPI dose schedule to CM8HW (IPI only given for four doses Q3W). Similar outcomes have been demonstrated in real world evidence comparing NIVO + IPI with immunotherapy monotherapy in other indications, as well as indirect comparisons.[85,86]

B.2.5 Subgroup analysis

B.2.5.1 CheckMate 8HW

The centrally-confirmed population was stratified by tumour-sidedness in a prespecified subgroup analysis; PFS per BICR was consistent across subgroups [redacted] using the Gail-Simon test).[114]

In addition, the primary endpoint (PFS per BICR in the centrally confirmed population) was analysed across pre-specified subgroups in the centrally-confirmed population. Table 29 presents selected subgroup analysis; across all subgroups, the HRs significantly favoured NIVO + IPI over chemotherapy.

Across mutation subgroups, the efficacy of NIVO + IPI was comparable to the total population efficacy (centrally confirmed). PFS was not reached in the NIVO + IPI arm for the total centrally confirmed population, the BRAF mutation subgroup and the

KRAS/NRAS mutation subgroup; in the chemotherapy arm, median PFS was 5.9 months, 9.2 months and 5.7 months in these groups respectively, with HRs of 0.21, 0.37 and 0.24.

Table 29. CM8HW subgroup analysis for PFS in centrally confirmed population (interim analysis)[114,118]

		NIVO + IPI		Chemotherapy	
	N	PFS (95% CI)	N	PFS (95% CI)	HR (95% CI)
Age					
< 65	[redacted]	NR [redacted]	[redacted]	5.68 [redacted]	0.19 [redacted]
≥ 65	[redacted]	NR [redacted]	[redacted]	5.85 [redacted]	0.24 [redacted]
≥ 65 and < 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region					
US/Canada/ Europe	[redacted]	NR [redacted]	[redacted]	5.68 [redacted]	0.27 [redacted]
Asia	[redacted]	NR	[redacted]	7.39 [redacted]	0.03 [redacted]
Rest of world	[redacted]	NR [redacted]	[redacted]	6.21 [redacted]	0.16 [redacted]
ECOG PS					
0	[redacted]	NR [redacted]	[redacted]	9.00 [redacted]	0.22 [redacted]
1	[redacted]	NR [redacted]	[redacted]	4.21 [redacted]	0.20 [redacted]
Liver metastasis					
Yes	[redacted]	NR [redacted]	[redacted]	5.85 [redacted]	0.11 [redacted]
No	[redacted]	NR [redacted]	[redacted]	5.36 [redacted]	0.28 [redacted]
PD-L1 status					
≥ 1%	[redacted]	NR [redacted]	[redacted]	3.35 [redacted]	0.11 [redacted]
<1%	[redacted]	NR [redacted]	[redacted]	6.47 [redacted]	0.22 [redacted]
Mutation status					
BRAF/KRAS/NRAS WT	[redacted]	34.30 [redacted]	[redacted]	5.36 [redacted]	0.08 [redacted]

BRAF mutant	[redacted]	NR[redacted]	[redacted]	9.23[redacted]	0.37[redacted]
KRAS or NRAS mutant	[redacted]	NR[redacted]	[redacted]	5.68[redacted]	0.24[redacted]

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; NA, not available; NIVO, nivolumab; PD-L1, programmed death ligand 1

B.2.5.1.1 Post-hoc chemotherapy subgroup analysis

As noted previously, a high proportion of patients in the chemotherapy arm received a bevacizumab containing regimen (n=56; 63.6% treated population; 55.4% randomised population).[116] As bevacizumab is not reimbursed for use in UK clinical practice in this indication, subgroup analyses have been conducted which exclude patients who received bevacizumab. Additionally, as panitumumab-containing regimens are not included in CM8HW, but are used in UK clinical practice for patients with RAS wildtype mCRC,[71] subgroup analyses for patients receiving cetuximab containing regimens have been explored. It should be noted that it has been previously established that panitumumab and cetuximab may be considered to have comparable efficacy (TA709).[1]

Baseline characteristics (Table 30) show some imbalances between patients who received bevacizumab- or cetuximab-containing regimens and patients who did not. There is a particular disparity concerning negative prognostic factors; [redacted] of patients who received bevacizumab- or cetuximab-containing regimens had liver metastases, compared with [redacted] in those who did not. Additionally, [redacted] and [redacted] of cases were diagnosed at stage IV in these groups respectively. In addition, the incidence of these prognostic factors is markedly lower in the 'no bevacizumab or cetuximab' cohort compared with patients receiving NIVO + IPI.

Efficacy results presented in Table 31 relate to PFS per BICR for all randomised subjects. Patients receiving chemotherapy regimens without bevacizumab or cetuximab show a substantially lower median PFS when compared with patients receiving bevacizumab-containing regimens ([redacted] months vs. [redacted] months, respectively). The median PFS among patients receiving cetuximab-containing regimens is also notably low ([redacted] months); however, results for this cohort should be interpreted with particular caution due to low sample size.

Table 30. CM8HW baseline characteristics (chemotherapy subgroup analysis)

		Bevacizumab containing regimen (n=56)	Cetuximab containing regimen (n=11)	No bevacizumab or cetuximab (n=34)	All chemotherapy (n=101)
ECOG performance status, n (%)	0	[redacted]	[redacted]	[redacted]	52 (51.5)
	≥1	[redacted]	[redacted]	[redacted]	[redacted]
Primary tumour sidedness, n (%)	Left	[redacted]	[redacted]	[redacted]	[redacted]
	Right	[redacted]	[redacted]	[redacted]	68 (67.3)
Prior surgery related to current cancer, n (%)	Yes	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior systemic cancer therapy regimens received, n	0	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]
	≥2	[redacted]	[redacted]	[redacted]	[redacted]
Liver metastasis, n (%)	Yes	[redacted]	[redacted]	[redacted]	36 (35.6)
	No	[redacted]	[redacted]	[redacted]	[redacted]
	Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Lung metastasis, n (%)	Yes	[redacted]	[redacted]	[redacted]	19 (18.8)
	No	[redacted]	[redacted]	[redacted]	[redacted]
	Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Disease stage at diagnosis, n (%)	Stage II	[redacted]	[redacted]	[redacted]	[redacted]
	Stage III	[redacted]	[redacted]	[redacted]	[redacted]
	Stage IV	[redacted]	[redacted]	[redacted]	49 (48.5)
BRAF/KRAS/NRAS mutation status, n (%)	BRAF/KRAS/NRAS all WT	[redacted]	[redacted]	[redacted]	23 (22.8)
	BRAF mutant	[redacted]	[redacted]	[redacted]	24 (23.8)
	KRAS/NRAS mutant	[redacted]	[redacted]	[redacted]	21 (20.9)
	BRAF and KRAS/NRAS mutant	[redacted]	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]	31 (30.7)
	dMMR	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: dMMR, DNA mismatch repair deficiency; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; MMR, DNA mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatellite stable; NIVO, nivolumab; pMMR, DNA mismatch repair proficiency; WT, wildtype

Table 31. CM8HW PFS results for all randomised subjects per BICR (interim chemotherapy sub-group analysis)

		Bevacizumab containing regimen	Cetuximab containing regimen	No bevacizumab or cetuximab	Chemotherapy
N		56	[redacted]	[redacted]	101
PFS (BICR)	Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Median (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]
PFS rate, % (95% CI)	6 months	[redacted]	[redacted]	[redacted]	[redacted]
	12 months	[redacted]	[redacted]	[redacted]	[redacted]
	24 months	[redacted]	[redacted]	[redacted]	[redacted]

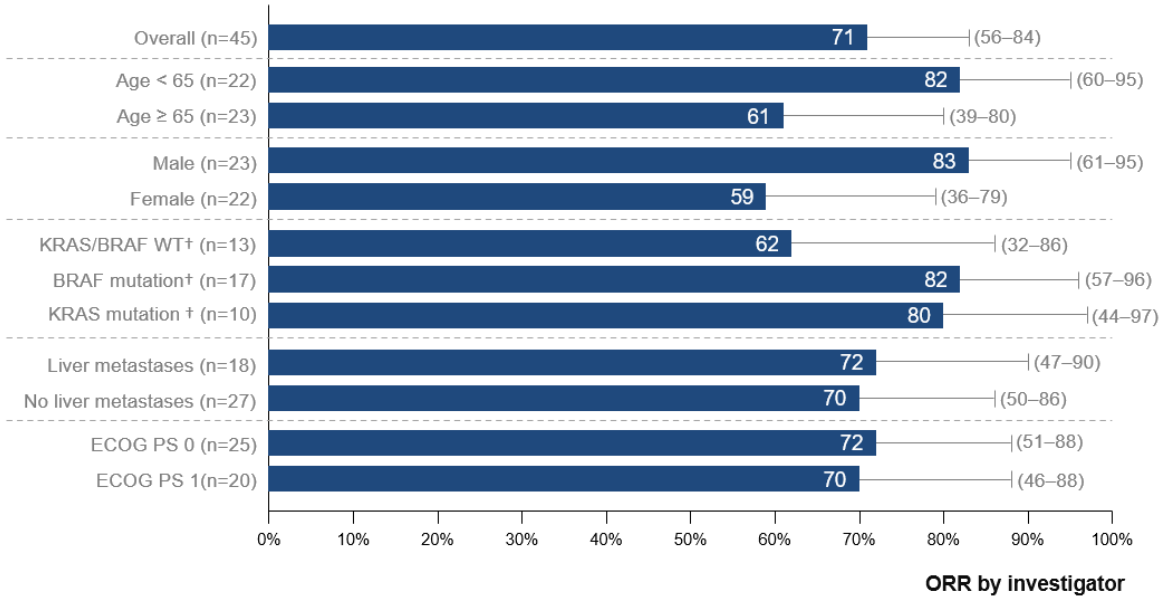
BICR, blinded independent central review; PFS, progression free survival

B.2.5.2 CheckMate 142

B.2.5.2.1 ORR

ORR was analysed across pre-specified subgroups with sufficient populations; across all analyses, the 95% CIs for ORR overlapped, demonstrating that ORR was not significantly different across subgroups (Figure 15, Table 32).

Figure 15. CM142 subgroup analysis for ORR tornado plot[121]



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ORR, overall response rate

†Excludes 5 patients with unknown mutation status

Table 32. CM142 subgroup analysis for ORR[121]

	NIVO+ IPI (n = 45)	95% CI
Age, years		
< 65 (n = 22)	82	60–95
≥ 65 (n = 23)	61	39–80
Sex		
Male (n = 23)	83	61–95
Female (n = 22)	59	36–79
Mutation status		
KRAS/BRAF WT (n = 13)	62	32–86
BRAF mutation (n = 17)	82	57–96
KRAS mutation (n = 10)	80	44–97
Liver metastases		
Yes (n = 18)	72	47–90
No (n = 27)	70	50–86
ECOG PS		
0 (n = 25)	72	51–88
1 (n = 20)	70	46–88

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; NIVO, nivolumab; ORR, overall response rate

B.2.5.2.2 PFS and OS

PFS and OS were analysed across pre-specified subgroups with sufficient populations. In patients with KRAS/BRAF WT, median PFS was 44.7 months; PFS was not reached in patients with KRAS or BRAF mutations. OS was not reached for either subgroup.[121]

In patients with liver metastases (n = 18), median PFS was 44.3 months. PFS was not reached in those without liver metastases (n = 27). Median OS was not reached in either subgroup.[121] However, PFS data should be interpreted with caution due to very low patient numbers at 42 months (liver metastases n = 6).

B.2.6 Meta-analysis

Evidence from CM8HW and CM142 is presented Section B.2.2 to B.2.5. Indirect comparisons are presented in Section B.2.7.

B.2.7 Indirect and mixed treatment comparisons

In the absence of direct clinical trial evidence for NIVO+IPI versus PEMBRO, an indirect comparison is required. Although direct trial evidence is not available for NIVO + IPI versus panitumumab with chemotherapy, direct evidence is available for NIVO + IPI versus cetuximab with chemotherapy, which NICE has previously concluded has comparable efficacy to panitumumab (TA709). Despite this conclusion, an ITC scenario analysis has been conducted to inform a comparison of NIVO+IPI versus panitumumab.

As outlined in Section B.2.1 and Appendix D, an SLR has been conducted to identify relevant evidence in a population of previously untreated patients with dMMR/MSI-H mCRC. This study identified one study providing clinical evidence for PEMBRO: KN-177. The population, intervention, comparison, outcomes, and study (PICOS) criteria can be found in Table 33.

Based on this SLR, one study (KN-177) was identified that provided outcomes for PEMBRO versus chemotherapy in previously untreated patients with dMMR/MSI-H mCRC. No studies were identified for panitumumab in previously untreated patients with dMMR/MSI-H mCRC specifically. However, outside of the scope of the SLR,

one study (PRIME) was identified for panitumumab plus FOLFOX versus chemotherapy in previously untreated patients with mCRC (i.e., regardless of dMMR/MSI-H status).[124] This study was identified from TA709[1] where it was considered appropriate to inform the ITC with comparative efficacy data for panitumumab.

Table 34 provides an overview of the available studies. Using these studies, a feasibility assessment was undertaken to identify the most appropriate methods for indirect comparison.

Table 33. SLR PICOS criteria

PICOS elements	Inclusion criteria
Population	Adults (≥ 18 years) and adolescents (≥ 12 years) with previously untreated unresectable or metastatic dMMR/MSI-H CRC
Intervention/ comparator	• Nivolumab plus ipilimumab • Pembrolizumab • Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Capecitabine plus oxaliplatin (CAPOX) • Capecitabine • Folinic acid plus fluorouracil plus oxaliplatin plus irinotecan (FOLFOXIRI) • Panitumumab with FOLFOX or FOLFIRI • Cetuximab with FOLFOX or FOLFIRI • Standard of care†
Outcome	• Overall survival • Progression free survival • Time to progression • Recurrence free survival • Time to treatment failure • Overall response rate, complete response, partial response, stable disease, duration of response • Adverse events • Mortality
Study design	• Phase 2-4 clinical trials • Randomised, non-randomised or single-arm controlled trials

†Standard of care defined as investigators choice should be included where treatment is one of the relevant listed intervention/comparator treatments.

Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficient; MSI-H, microsatellite instability high

Table 34. Relevant comparative trials identified for ITC

Trial Name	Start year	Cohort size	Follow-up	Intervention	Comparator
Identified in SLR					
CheckMate 8HW[118] (NCT04008030)	2019	831	Median: 24.9 months (NIVO + IPI), Median: 17.2 months (SoC), Median: 22.5 months (overall)	NIVO+IPI, NIVO	SoC
KEYNOTE-177[125] **(NCT02563002)**	2016	307	Median: 32.4 months	PEMBRO	SoC
Not in SLR eligible population (mCRC not specific to MSI-H/dMMR)					
PRIME[124] (NCT00364013)	2006	1183	Maximum: 109 weeks	FOLFOX + Panitumumab	SoC (FOLFOX)

Abbreviations: dMMR, DNA mismatch repair deficient; IPI, ipilimumab; MSI-H, microsatellite instability high; NIVO, nivolumab; PEMBRO, pembrolizumab; SoC, standard of care

B.2.7.1 ITC feasibility assessment for NIVO + IPI versus PEMBRO

The full ITC feasibility assessment can be found in Appendix M. A brief overview of the assessment is provided within this submission.

Only one RCT identified by the SLR was conducted in a similar patient population compared to CM8HW, i.e., the dMMR/MSI-H mCRC population. As such, KN-177 was considered as the key study of interest for the ITC. KN-177 investigated the efficacy of PEMBRO compared with chemotherapy in locally confirmed dMMR/MSI-H mCRC. A network of evidence can be drawn connecting CM8HW with KN-177 via the common comparator (SoC; chemotherapy).

The feasibility assessment reviewed predominantly i) the similarity of studies (following the PICOS criteria) and ii) the validity of the proportional hazards assumption (PHA) to assess whether an ITC would be feasible. Based on these criteria, suitable approaches were recommended.

The similarity assessment revealed that CM8HW and KN-177 were comparable in terms of inclusion and exclusion criteria, the common comparator (chemotherapy) treatments, outcome definitions and study design. Furthermore, the two trials were comparable across most of the baseline characteristics assessed, including patient characteristics identified by clinical experts as most relevant for mCRC.[126]

The PHA testing for the KN-177 PFS data was performed using the pseudo-individual patient-level data generated from the published KM curves. The PHA was violated, indicating that constant HR-based ITC methods may be biased.

Based on the feasibility assessment, three approaches were recommended for the ITC:

- Fractional polynomial network meta-analysis (NMA), which does not require adjustment of data and does not require the PHA.
- Anchored or non-anchored MAIC, which allows for the adjustment of present heterogeneity in treatment effect modifiers without requiring the PHA to hold
- HR-based NMA to serve as a scenario analysis, even though PHA is violated

However, in the context of violated PHA and minor differences in patient population, the fractional polynomial NMA is considered to be most appropriate and is provided as the ITC base case analysis. Alternative methodology has been considered, and these are provided as a scenario analysis.

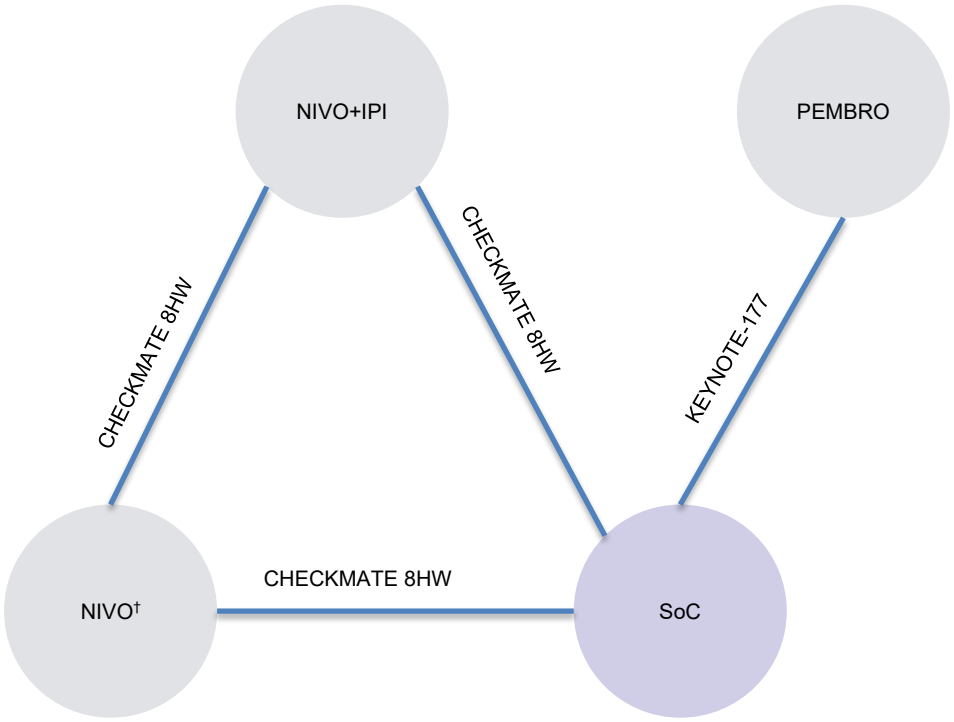
B.2.7.2 Fractional polynomial NMA

A full description of the methodology and outcomes for the fractional polynomial NMA (FPNMA) is provided as Appendix N1. A brief overview is provided within this submission.

B.2.7.2.1 Methodology

Based on results of the SLR and feasibility assessment, the following connected network can be formed between NIVO+IPI, NIVO, and PEMBRO with all nodes connecting to standard of care (SoC; Figure 16). An additional network geometry, including the PRIME study, which will be used for sensitivity analysis, can be viewed in Figure 17.

Figure 16. Network of relevant evidence identified by SLR



Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; SoC, standard of care
†Data from the NIVO arm of the CheckMate 8HW trial are not available and would not be included in the ITC network, as they provide no new information to inform the ITC between NIVO+IPI and PEMB.
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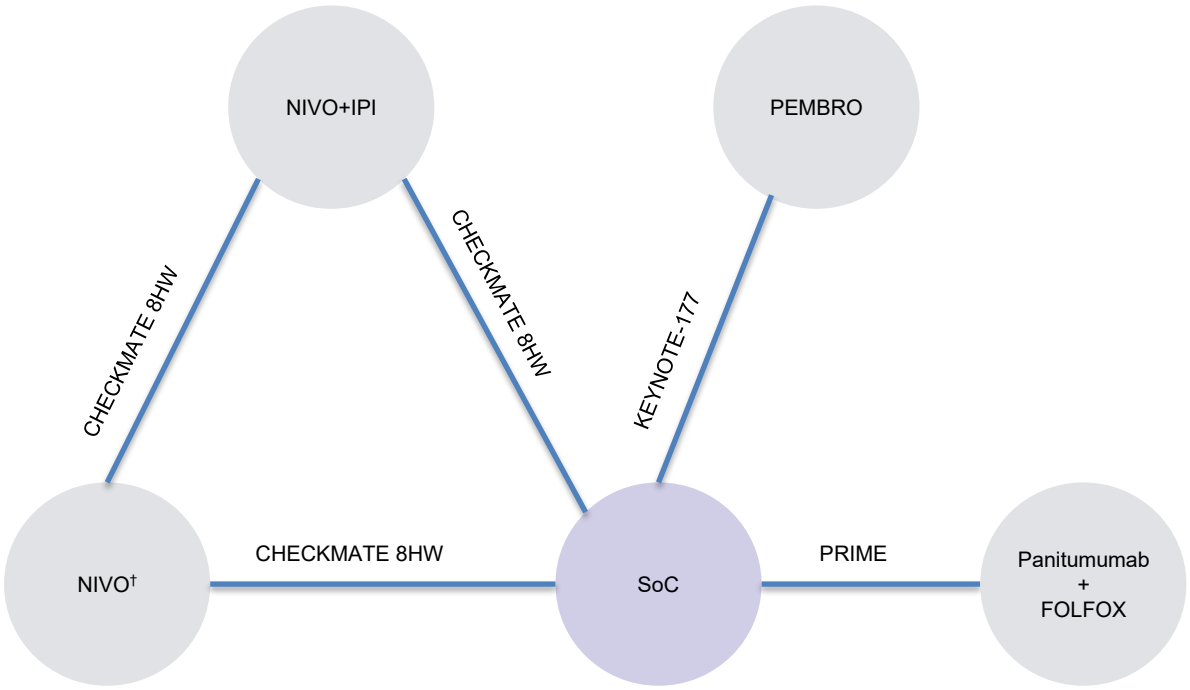
Figure 17. Network of evidence to be used for sensitivity analysis



Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; SoC, standard of care.
†Data from the NIVO arm of the CheckMate 8HW trial are not available and would not be included in the ITC network, as they provide no new information to inform the ITC between NIVO+IPI and PEMB.

Analysis of PFS involved fractional polynomial FP NMA which are flexible and can model HRs as being constant over time or time varying. The main outputs of the FP NMA were HRs at each time, t (in months), and associated credible intervals (CrIs) over a 60-month time horizon.

Absolute model fit was considered through examination of the total residual deviance, in keeping with NICE DSU guidelines[127]. The deviance information criterion (DIC) was used to compare the fit of the different models with the same likelihood (e.g., fixed and random effects models). The DIC considers the absolute fit of the model, whilst adding a penalty for model complexity. Lower values of the DIC suggest a more parsimonious model; this informed which models were given most weight when interpreting the results. It is generally considered that a difference in DIC of 3-5 suggests a meaningful difference in model fit.[127]

Both fixed effects models and random effects models were considered. However, random effects models provided spurious results and were not considered further.

With respect to safety outcomes, a simple Bayesian fixed-effects binomial model with logit link was used to determine whether there were any differences in the incidence of AEs between treatments on the network.

B.2.7.2.2 Outcomes

B.2.7.2.2.1 PFS

Under the convergence and computational limits applied, 86 of the 161 candidate fixed-effects models converged (as assessed by a criterion of Rhat > 1.01). Of the 75 models that did not converge, 9 were first order, with the remaining 66 second order. Among the models that converged, the 20 with lowest DIC underwent inspection of the traces, posterior distributions and survival predictions. All models were accepted as converged and plausible within follow-up.

Table 35. Fixed effects model selection by DIC, PFS, primary network

Selection	Model	DIC	Maximum Rhat	N iterations / samples
Primary analysis	[redacted]	[redacted]	[redacted]	[redacted]
First sensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Second sensitivity	[redacted]	[redacted]	[redacted]	[redacted]
First rejection	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; PFS, progression-free survival

Time-varying hazard ratios for NIVO + IPI versus all comparators are presented in Table 36. Versus PEMBRO, the credible interval for the hazard ratio favours NIVO + IPI and excludes 1 at all landmark times, indicating significantly lower hazard at these times in the primary and second sensitivity models. Under the primary analysis and second sensitivity models, the hazard ratio of NIVO + IPI versus PEMBRO is predicted to increase from 6 months to 60 months (increasing treatment effect), though this increase is noted to be very gradual, particularly from 36 months for the primary analysis. For the first sensitivity model, treatment effect is predicted at a maximum around between 6 and 24 months and decreases slowly thereon.

The log hazard functions at posterior median parameters inferred by the FPNMA models were used to estimate survival upon each study baseline, as shown in Figure 19. Model fits to within-trial treatment arms are good and indicate that all three fractional polynomial models are flexible enough to represent the hazard profiles observed in the source data. For prediction out of study, PEMBRO is predicted to have slightly lower PFS in CheckMate 8HW and NIVO + IPI is predicted to have slightly higher PFS in KN-177, reflecting the difference in SoC PFS between these trials.

Table 36. PFS hazard ratios–- NIVO + IPI versus all comparators – Primary network

Selection / Model	NIVO + IPI vs …	HR (95% CrI) at month					
		6	12	24	36	48	60
Primary analysis / Net1_-0.5_-0.5_1 10	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First sensitivity / Net1_-0.5_-0.5_1 11	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second sensitivity / Net1_-1_0_1 10	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval' HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; SoC, standard of care

Figure 18. PFS hazard ratios–- NIVO + IPI versus all comparators – Primary network–- Primary model

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival; SoC, standard of care

Figure 19. PFS prediction via fractional polynomial models–- Primary network–- Primary model

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival; SoC, standard of care

B.2.7.2.2.2 Adverse events

Log odds ratios of incidence of any AE for NIVO + IPI versus all comparators in the primary network under a fixed-effects analysis are reported in Table 37.

In comparisons of NIVO + IPI vs PEMBRO, the credible interval is inclusive of 0, indicating no significant difference, with the exception of TRAEs of grade ≥3 where NIVO + IPI is inferred to have higher odds. This reflects the large difference in AE incidence in the SoC arms across the two trials; however, this difference is not reflected in the immunotherapy arms, which have very similar AE incidence rates.

Table 37. Log odds ratios of incidence of any adverse event–- fixed effects–- primary network

Outcome	Log odds ratio (95% CrI)	
	NIVO + IPI vs SoC	NIVO + IPI vs PEMBRO
Any AE	[redacted]	[redacted]
Any AE grade ≥3	[redacted]	[redacted]
Any TRAE	[redacted]	[redacted]
Any TRAE grade ≥3	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]

Abbreviations: AE, adverse events; CrI, credible interval; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TRAE, treatment-related adverse event

B.2.7.2.2.3 Scenario analysis versus panitumumab

B.2.7.2.2.3.1 PFS

An overview of model selection is provided in Appendix N1.

Time-varying hazard ratios for NIVO + IPI versus all comparators are presented in Table 38. Versus PEMBRO, the results are consistent with the primary network.

Versus panitumumab + FOLFOX, all models predicted an increasing and significant hazard ratio over 6–60 months.

The log hazard functions at posterior median parameters inferred by the FPNMA models were used to estimate survival upon each study baseline; these survival predictions are shown in Figure 21

Table 38. PFS hazard ratios–- NIVO + IPI versus all comparators – Sensitivity network

Selection / Model	NIVO + IPI vs …	HR (95% CrI) at month					
		6	12	24	36	48	60
Primary analysis / Net2_-0.5_-0.5_1 11	SoC	[redacted]					
	PEMBRO	[redacted]					
	PAN + FOLFOX	[redacted]					
First sensitivity / Net2_-0.5_-0.5_1 10	SoC	[redacted]					
	PEMBRO	[redacted]					
	PAN + FOLFOX	[redacted]					
Second sensitivity / Net2_-1_0_1 11	SoC	[redacted]					
	PEMBRO	[redacted]					
	PAN + FOLFOX	[redacted]					

Abbreviations: CrI, credible interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PAN, panitumumab; PEMBRO, pembrolizumab; PFS, progression-free survival

Figure 20. PFS hazard ratios–- NIVO + IPI versus all comparators – Sensitivity network–- Primary model

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; SoC, standard of care

Figure 21. PFS prediction via fractional polynomial models–- Sensitivity network–- Primary model

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; SoC, standard of care

B.2.7.2.2.3.2 Adverse events

Log odds ratios of incidence of any AE for NIVO + IPI versus all comparators in the primary network under a fixed-effects analysis are reported in Table 39. Only comparisons where data were available from PRIME were evaluated. Panitumumab + FOLFOX shows greater odds of any AE grade ≥3 compared with NIVO + IPI, as well as greater odds of diarrhoea and neutropenia.

Table 39. Log odds ratios of incidence of any adverse event–- fixed effects–- sensitivity network

Outcome	Log odds ratio (95% CrI)		
	NIVO + IPI vs SoC	NIVO + IPI vs PEMBRO	NIVO + IPI vs PAN + FOLFOX
Any AE	[redacted]	[redacted]	[redacted]
Any AE grade ≥3	[redacted]	[redacted]	[redacted]
Any TRAE	[redacted]	[redacted]	[redacted]
Any TRAE grade ≥3	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CrI, credible interval; IPI, ipilimumab; NIVO, nivolumab; PAN, panitumumab; PEMBRO, pembrolizumab; TRAE, treatment-related adverse event

B.2.7.2.3 Conclusions

This analysis found that hazard of progression or death is reduced by use of NIVO + IPI versus SoC, PEMBRO and panitumumab + FOLFOX. This was consistently found to be statistically significant up to 12 months against all treatments, and for treatments other than PEMBRO, up to 60 months. For PEMBRO, all models predict a sustained and stabilising hazard ratio of progression or death from month 12 to month 60.

In the primary network and with the primary model, the PFS HRs for NIVO + IPI versus PEMBRO varied from [redacted] (95% CrI [redacted]) at 6 months to [redacted] (95% CrI [redacted]) at 60 months. These values are favourable in comparison to the values generated using the anchored MAIC (Appendix N2), which in turn predicted larger benefit for NIVO + IPI than the non-anchored MAIC. Unlike those models, the best-fitting fractional polynomial models do not predict a substantial trend towards reduction of the HR treatment effect. Values of the HR from 6 months onwards are substantially below that of the constant HR NMA, reflecting the influence of the early data on the Cox proportional hazards model.

Despite numerically similar investigational arm adverse event incidence rate between CM8HW and KN-177, there were substantial differences in control arm TRAEs of grade ≥3, which calls into question the assumption of transitivity of log odds differences across the network. Despite this, outcomes from this ITC are similar to those from previous comparisons of NIVO + IPI and PEMBRO, which found that the safety profile was not statistically significantly different between NIVO + IPI and PEMBRO, with the potential exception of grade ≥ 3 TRAEs.[85,128,129]

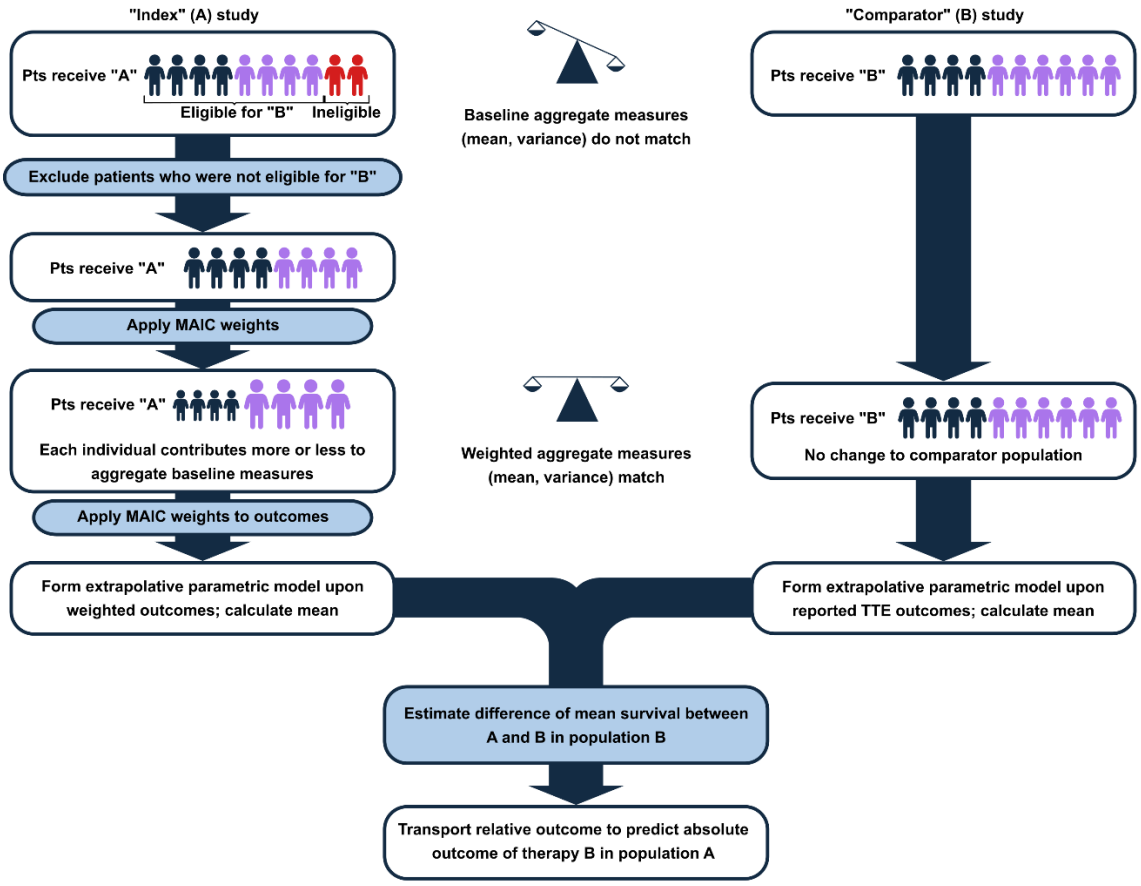
B.2.7.3 MAIC

Full methodology is provided in Appendix N2, with a brief overview provided below.

Matching-adjusted indirect comparison (MAIC) is a population-adjusted treatment comparison method to adjust for cross-study differences in clinically relevant treatment effect modifiers. MAIC recalculates the efficacy of the treatment (i.e., NIVO + IPI), assuming the drug is used in patient populations similar to those of the respective comparator trial (population of KN-177). The MAIC methodology is described in detail in the NICE Decision Support Unit (DSU) Technical Support Document 18.[15] The matching methodology is designed to statistically construct trial patient populations which are similar to one another, such that the outcomes from different trials can be meaningfully compared. Figure 22 provides an overview of the process.

Seven treatment effect modifiers (age, ECOG PS, BRAF/KRAS/NRAS mutation status, tumour sidedness, liver metastasis, liver or lung metastasis, and region) were identified based on expert opinion of relevant baseline characteristics in mCRC.[126]

Figure 22. The MAIC process (Atkins et al. 2017.) [130]



Abbreviations: MAIC, matching-adjusted indirect comparison

Baseline characteristics before and after matching for CM 8HW to KN-177 are provided in Table 40. Most treatment effect modifiers (TEM) were comparable between CM 8HW and KN-177 before matching, with differences between trials ≤ 3%. However, the regional distribution of patients between the trials differed, with fewer Asian and Western European/North American patients, and more patients from other regions, in CM8HW compared with KN-177. Matching balanced all seven TEMs, including region. Post-matching, the regional distribution of patients in adjusted CM 8HW appeared to be similar to that of KN-177.

Table 40. Summary of patient characteristics included in the MAIC – CM8HW and KEYNOTE-177 populations

Treatment effect modifiers	KN-177 (N = 307)	CM8HW	
		Unadjusted (N = 303)	Matched (N = 241.7)
Age, in years, median (min, max)	63 (24, 93)	63 (21, 87)	[redacted]
ECOG PS 0, n (%)	159 (52)	163 (54)	[redacted]
BRAF/KRAS/NRAS mutation status, n (%)			
BRAF, KRAS, NRAS all wild type	69 (22)	70 (23)	[redacted]
KRAS or NRAS mutant†	74 (24)	71 (23)	[redacted]
BRAF mutant†	77 (25)	83 (27)	[redacted]
Could not be evaluated	90 (29)	86 (28)	[redacted]
Site of primary tumour (sidedness), n (%)			
Right	219 (71)‡	205 (68)	[redacted]
Left	88 (29)	98 (32)	[redacted]
Liver metastasis, n (%)	125 (41)	118 (39)	[redacted]
Liver or lung metastasis, n (%)	159 (52)	156 (51)	[redacted]
Region, n (%)			
Asia	48 (16)	30 (10)	[redacted]
Western Europe/North America§	222 (72)	178 (59)	[redacted]
Rest of the world	37 (12)	95 (31)	[redacted]

†Three patients from KEYNOTE-177 and seven patients from CM8HW who had both a BRAFV600E mutation and a KRAS or NRAS mutation are included. Totals will not add up to 100%

‡Includes 10 patients who were classified 'both sided'

§CM8HW reported 'US/Canada/Europe' patients from Czech Republic and Romania were reclassified to the rest of the world.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; MAIC, matching-adjusted indirect comparison; N, Number of subjects in the unadjusted analysis set

When comparing the weighted and unweighted KM curves, weighting did not change the PFS estimates significantly, as shown in Figure 23. PFS per BICR is the CM 8HW analysis applied across all ITC methodologies.

Figure 24 shows the weighted KM curves. Upon weighting, the NIVO + IPI arm shifted slightly upwards from around 6 months of follow-up; the chemotherapy arm

also shifted upwards, but to a lesser extent. This upward shift is only apparent towards the end of the follow-up period, from around 12 months. The Cox proportional hazards-based HR only changed slightly (improving to 0.31 from [redacted] upon weighting). Table 41 shows the HRs (with 95% CI) for CM 8HW before and after matching.

Figure 23. KM curves for PFS in CM8HW before and after matching

Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; PFS, progression-free survival

Figure 24. Weighted KM curves for PFS (CM8HW and KEYNOTE-177)

Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; PFS, progression-free survival

Table 41 HRs and 95% CI for CM8HW before and after matching

CM 8HW (NIVO + IPI vs Chemotherapy)	HR (95% CI)
Unweighted	0.32 (0.22, 0.46)
Weighted to KN-177	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab

Following weighting, survival was extrapolated using parametric survival curves fitted to each treatment arm of both trials. The parametric distributions fitted to the trial were the exponential, gamma, generalised gamma, Gompertz, log-logistic, lognormal and Weibull distributions. The selection of extrapolation models was based on statistical fit of the models to the trial data, based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC) scores, as well as visual inspection of the survival curves and hazard plots. Generalised gamma parameterisations were selected for all four treatment arms, based on these selection criteria, provided in Figure 25.

Figure 25. PFS KM curves and extrapolated best-fitting distributions

Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; PFS, progression-free survival

The fitted parametric distributions were utilised to estimate hazards and their standard errors over time. Based on these, time-varying HRs for each time point of the extrapolation were estimated, along with 95% CIs. These estimated time-varying PFS HRs for CM8HW and KN-177 are shown in Figure 26.

The time-varying HRs for both trials were greater than 1 in the first months, demonstrating an early peak. The HRs then drop below 1 and remain for the rest of the extrapolated period for both trials. The HR for weighted PFS in CM8HW reaches a minimum of approximately [redacted] at 12 months, with the HR for KN-177 also reaching its minimum of approximately 0.35 at a similar time. The HRs for both trials are seen to steadily increase after 12 months. The 95% CIs are largely non-overlapping during the initial 24 months, after which the 95% CIs show considerable overlap.

Figure 26. Time-varying hazard ratios for weighted CM8HW and KEYNOTE-177

B.2.7.3.1 MAIC (unanchored)

In addition to the anchored MAIC, an unanchored MAIC was conducted as a scenario analysis and for validation purposes. Full methodology and results are reported in Appendix N3.

The methodology for deriving MAIC weights is similar for the anchored and unanchored analysis, the only difference in the unanchored analysis is that matching weights are derived only for the NIVO + IPI arm of CM 8HW, and the SoC chemotherapy arms of both trials are left out of the analysis. As randomization is not preserved in an unanchored analysis, matching is performed based on both the treatment effect modifiers (as per anchored MAIC) and prognostic variables identified from the literature (Appendix N3).

Extrapolated PFS for NIVO + IPI and PEMBRO (based on the generalized gamma function) is presented in Figure 27 and predicted 5- and 10-year landmark PFS estimates presented in Table 42. Results indicate NIVO + IPI is favourable compared to PEMBRO in both analyses. However, compared to the anchored MAIC results, the unanchored analysis presents a more conservative estimate of NIVO + IPI PFS compared with PEMBRO, with a constant HR of [redacted] in the weighted unanchored analysis vs. [redacted] in the weighted anchored MAIC.

Figure 27. PFS KM curves and extrapolated best-fitting distributions – comparison between anchored and unanchored MAIC for NIVO + IPI arm

Table 42. Landmark PFS estimates–- comparison between anchored and unanchored MAIC for NIVO + IPI arm

Estimated landmark survival, %	5-year estimate	10-year estimate
NIVO + IPI (weighted, unanchored)	[redacted]	[redacted]
NIVO + IPI (weighted, anchored)	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PEMBO, pembrolizumab; PFS, progression-free survival

B.2.7.4 Constant hazard NMA

A constant HR-based NMA was performed as a scenario analysis, as described in Appendix N2. It is acknowledged that this analysis should be interpreted with caution, as the PHA is violated. However, the approach is presented for completeness and as a validation exercise.

The analysis used published KN-177 PFS hazard ratios from 5-year follow-up data[9] (HR: 0.60 [95% CI 0.45 – 0.79]) and the outcomes from CM8HW:

- unstratified HR of weighted CM 8HW data (HR: [redacted]) output from the MAIC in Section B.2.7.3.

- unstratified HR of unweighted CM 8HW data (HR: 0.32 [0.22, 0.46])

Outcomes are presented in Table 43 and Table 44. Outcomes are similar between the weighted and unweighted analysis, indicating that weighting had limited impact. For the weighted analysis, the fixed effect Bayesian HR-based NMA estimated a posterior HR and 95% CrIs for NIVO + IPI vs PEMBRO of [redacted] and versus chemotherapy of [redacted] This is suggestive of a beneficial effect of NIVO + IPI in the studied population, as the estimated 95% CrIs do not cross 1.

As demonstrated in Figure 28, outcomes from the constant hazard NMA are aligned with outputs from the MAIC analysis.

Table 43. Fixed effect Bayesian NMA: weighted CM8HW data (hazard ratio and 95% credible intervals)

Treatment	Chemotherapy	NIVO + IPI	PEMBRO
Chemotherapy	[redacted]	[redacted]	[redacted]
NIVO + IPI	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab

Table 44. Fixed effect Bayesian NMA: unweighted CM8HW data (hazard ratio and 95% credible intervals)

Treatment	Chemotherapy	NIVO + IPI	PEMBRO
Chemotherapy	[redacted]	[redacted]	[redacted]
NIVO + IPI	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab

Figure 28. Comparison of MAIC-adjusted ITC hazard ratio and constant hazard NMA for NIVO + IPI vs PEMBRO

Pink line represents MAIC adjusted HR. Green dotted line represents constant HR approach

Abbreviations: IPI, ipilimumab; ITC, indirect treatment comparison; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab

B.2.7.5 Conclusions from the indirect comparison analysis

A summary of the indirect comparisons between NIVO + IPI and PEMBRO is provided in Table 45.

The anchored MAIC appears to be more favourable for NIVO+IPI in the initial stages of follow-up, while the unanchored MAIC and constant HR NMA provide more conservative estimates. The FP NMA provides the most robust estimate of comparative effectiveness, as it does not require adjustment of data and does not require the PHA. Additionally, it provides plausible outcomes, as shown in Figure 19. However, across approaches, there is a clear and consistent PFS benefit for NIVO + IPI over PEMBRO.

Table 45. NIVO + IPI versus PEMBRO PFS hazard ratios across ITC approaches

		HR (95% CrI) at month				
		12	24	36	48	60
FP NMA	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anchored MAIC	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant HR NMA	NIVO + IPI vs PEMBRO	[redacted]				

Abbreviations: CrI, credible interval; FP, fractional polynomial; IPI, ipilimumab; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab

B.2.7.6 Uncertainties in the indirect and mixed treatment comparisons

Comparative clinical efficacy would ideally be drawn from RCTs with active comparators, and where these are not available, the standard approach would be to conduct an NMA. However, in this case, the PHA is violated, so that a standard constant HR NMA is not appropriate. As a result, alternative methodologies have been considered, in line with NICE DSU guidance. All approaches have been considered and outcomes provided within this submission.

In the context of the minor differences in patient population, the fractional polynomial NMA is considered to be the most appropriate and is provided as the ITC base case analysis. However, PFS outcomes for the chemotherapy arm of CM8HW are numerically lower than for KN-177 between approximately 6 months and approximately 24 months, although not statistically significant (Figure 29). One possible rationale is slightly higher bevacizumab usage in KN-177, although this has limited impact on the comparison of NIVO + IPI versus chemotherapy, as shown in Table 31. Alternatively, chemotherapy outcomes in CM8HW may be impacted by crossover to NIVO + IPI, as PFS censors at subsequent treatment. However, results for PFS per BICR using the EMA definition, which does not apply censoring at subsequent anti-cancer therapy initiation, were consistent with the primary analysis (HR: [redacted] CI: [redacted]). Although this does not impact on the comparative effectiveness of NIVO + IPI versus chemotherapy, there are consequences for the

PFS differences between the chemotherapy arms within the NMA. The anchored MAIC and fractional polynomial NMA provide outcomes that are potentially favourable to NIVO + IPI due to efficacy differences within the chemotherapy arms. As a consequence, the unanchored MAIC was undertaken as a sensitivity analysis, demonstrating a more conservative benefit for NIVO + IPI.

Figure 29. PFS KM estimates from CM8HW and KN-177, SoC arms

Abbreviations: CI, confidence interval; HR. Hazard ratio; KM, Kaplan-Meier; NAR, number at risk; PFS, progression-free survival; SoC, standard of care

The MAIC technique attempts to adjust for differences in baseline characteristics between studies to allow for comparison. This method is reliant on reporting of baseline characteristics and it is possible that vital covariates may not have been reported, impacting on comparison and adjustment. This is in common with all studies where variables may be unobservable; removal of bias due to these factors is not possible within MAIC.

Despite these limitations, this ITC has been undertaken in a robust and transparent manner, with all relevant methodology and results reported. The ITC approaches provided similar estimates of benefit for NIVO + IPI, although some were more conservative. However, NIVO + IPI is associated with PFS benefit across all analyses; this benefit was apparent by 12 months and maintained at 60 months.

B.2.8 Adverse reactions

B.2.8.1.1 CheckMate 8HW

Overall, NIVO + IPI was associated with improved tolerability compared with chemotherapy, despite longer duration of treatment (median duration 13.5 months vs. 4.0 months). In the NIVO + IPI group, there were fewer total TRAEs (80.0% vs. 94.3%), fewer grade 3 or 4 TRAEs (23.0% vs. 47.7%), and fewer TRAEs leading to discontinuation (16.5% vs. 31.8%) (Table 47). In group randomised to NIVO + IPI, there were 2 deaths due to study drug toxicity, whereas in the group randomised to chemotherapy, there was one (Table 46). However, this was a crossover patient, and the death was attributed to NIVO + IPI treatment.[114,118]

Categories of drug-related select AE occurring in ≥15% of participants in the NIVO + IPI group were endocrine ([redacted] gastrointestinal ([redacted] hepatic ([redacted] and skin ([redacted] the only grade 3 or 4 drug-related select AEs occurring in ≥5% were endocrine ([redacted](Table 47).[114]

As confirmed by UK clinical experts, IMAEs are of particular importance to clinicians and relatively unexplored during mCRC appraisals to date.[2]
Hypothyroidism/thyroiditis (17.0%) was the only IMAE that occurred in ≥15% of participants (Table 47). No grade 3 or 4 IMAEs occurred in ≥5% of participants; the most common grade 3 or 4 IMAEs were diarrhoea/colitis (4.5%), adrenal insufficiency (3.5%) and hepatitis (3.0%).[118] Across IMAE categories, most events in the NIVO + IPI arm were manageable using established IMAE treatment algorithms, with resolution reported when immune-modulating medications (mostly systemic corticosteroids) were administered. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy. Additionally, of the three deaths attributed to NIVO + IPI, one was attributed pneumonitis, which was identified as an IMAE.[114]

Table 46. CM8HW mortality in all treated subjects*[114]*

N (%)	NIVO + IPI (n = 200)	Chemotherapy (n = 88)
Deaths	[redacted]	[redacted]
From disease	[redacted]	[redacted]

Due to study drug toxicity	[redacted]	[redacted]
Other	[redacted]	[redacted]
Unknown reason	[redacted]	[redacted]

Abbreviations: IPI, ipilimumab; NIVO, nivolumab

Table 47. CM8HW adverse events in all treated subjects[114,118]

N (%)	NIVO + IPI (n = 200)		Chemotherapy (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All-causality AEs	[redacted]	[redacted]	[redacted]	[redacted]
All-causality TRAEs	160 (80.0)	46 (23.0)	83 (94.3)	42 (47.7)
SAEs				
All	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related	38 (19.0)	32 (16.0)	17 (19.3)	14 (15.9)
AEs leading to discontinuation				
All	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs	33 (16.5)	23 (11.5)	28 (31.8)	9 (10.2)
TRAEs in ≥ 15% of subjects in either arm				
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Neutropoenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related select AEs				
Endocrine	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary	[redacted]	[redacted]	[redacted]	[redacted]
Renal	[redacted]	[redacted]	[redacted]	[redacted]
Skin	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity/ infusion reactions	[redacted]	[redacted]	[redacted]	[redacted]
All-cause IMAEs within 100 days of last dose, treated with immune modulating medication				
Diarrhoea/Colitis	13 (6.5)	9 (4.5)	1 (1.1)	0 (0.0)

Hepatitis	11 (5.5)	6 (3.0)	0 (0.0)	0 (0.0)
Pneumonitis	4 (2.0)	3 (1.5)	0 (0.0)	0 (0.0)
Nephritis/Renal Dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Rash	11 (5.5)	3 (1.5)	0 (0.0)	0 (0.0)
Hypersensitivity/ infusion reactions	[redacted]	[redacted]	[redacted]	[redacted]
All-cause IMAEs within 100 days of last dose, with or without immune modulating medication				
Adrenal Insufficiency	21 (10.5)	7 (3.5)	0 (0.0)	0 (0.0)
Hypophysitis	10 (5.0)	5 (2.5)	0 (0.0)	0 (0.0)
Hypothyroidism/ Thyroiditis	34 (17.0)	3 (1.5)	1 (1.1)	0 (0.0)
Diabetes Mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	18 (9.0)	0 (0.0)	1 (1.1)	0 (0.0)

Abbreviations: AE, adverse event; IMAE, immune modulated adverse event; IPI, ipilimumab; NIVO, nivolumab; SAE, serious adverse event; TRAEs, treatment-related adverse event

B.2.8.1.2 CheckMate 142

Overall, NIVO + IPI demonstrated good tolerability, and no new safety concerns were identified. There were 9 (20%) grade 3 or 4 serious TRAEs, 7 (16%) TRAEs leading to discontinuation, and one treatment-related death (Table 48).

The most common categories of TRAEs with potential immunologic aetiology were skin (49%), endocrine (29%), gastrointestinal (20%) and hepatic (11%). There were no grade 3 or 4 TRAEs with potential immunologic aetiology which occurred in ≥5% of participants; endocrine, gastrointestinal and hepatic TRAEs all occurred in 2 patients (4%).

Table 48. CM142 TRAEs[121]

	NIVO+ IPI (n = 45)	
	Any grade	Grade 3/4
Any TRAEs, n (%)	36 (80)	9 (20)
Serious	7 (16)	5 (11)
Leading to discontinuation	7 (16)	2 (4)
Treatment-related deaths	1 (2)	
Any TRAEs occurring in ≥ 10% of the population, n (%)		
Pruritus	17 (38)	0 (0)
Arthralgia	9 (20)	0 (0)
Hypothyroidism	8 (18)	1 (2)

Rash	7 (16)	0 (0)
Asthenia	7 (16)	1 (2)
Diarrhoea	7 (16)	0 (0)
Fatigue	7 (16)	0 (0)
Nausea	6 (13)	0 (0)
Lipase increased	5 (11)	0 (0)
Pyrexia	5 (11)	0 (0)
TRAEs with potential immunologic aetiology, n (%)		
Endocrine	13 (29)	2 (4)
Gastrointestinal	9 (20)	2 (4)
Hepatic	5 (11)	2 (4)
Pulmonary	2 (4)	1 (2)
Renal	1 (2)	0 (0)
Skin	22 (49)	0 (0)

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; TRAE, treatment-related adverse event

B.2.9 Ongoing studies

CM8HW remains ongoing. The next pre-planned analysis will be the other primary endpoint PFS per BICR (all lines) for NIVO + IPI vs. NIVO monotherapy, which was not tested at this interim analysis due to not reaching the required event numbers. Once the next interim analysis is triggered, if statistical criteria are met, the secondary endpoints ORR (all lines) and PFS (1L) will also be tested for this comparison. Subsequently, if criteria are met, ORR (1L) will be tested for NIVO + IPI vs. chemotherapy and NIVO + IPI vs. NIVO monotherapy. Subsequently, if criteria are met, OS will be tested for NIVO + IPI vs. NIVO monotherapy (1L, all lines) and NIVO + IPI vs. chemotherapy (1L).

If any of the above endpoints are not met, the endpoint (and subsequent endpoints) will be tested again at the next pre-planned interim analysis following testing hierarchy, or at the final analysis.

B.2.10 Interpretation of clinical effectiveness and safety evidence

B.2.10.1 Principal findings from the clinical evidence

Survival in mCRC is poor, especially when diagnosed at a late stage; fewer than 20% of people diagnosed at stage IV survive for more than 5 years.[43] In addition,

observational studies have shown that the majority of mCRC (> 50%) is diagnosed at stage IV in UK clinical practice,[12-14] potentially due to poor uptake of screening programmes, delays in reporting symptoms, and prevalence of non-specific symptoms.[45,57,63] MSI-H tumours in particular have demonstrated inferior response to chemotherapy and worse outcomes compared with MSS tumours.[7,26,92,102,103]

NIVO + IPI provides a highly efficacious alternative to chemotherapy in people with previously untreated dMMR/MSI-H mCRC. In the CM8HW interim analysis, median PFS was [redacted] in the NIVO + IPI arm in the centrally confirmed dMMR/MSI-H population, whereas median PFS was [redacted] months in the chemotherapy arm. Hence, the primary endpoint was met, demonstrating a statistically significant and clinically meaningful improvement.

Further, in CM142, NIVO + IPI treatment was associated with a strong and durable response, with an ORR of 70%, and DOR, PFS and OS not reached after a median of 64.2 months of follow-up. This demonstrates that PFS benefits with NIVO + IPI can be expected to persist long-term, translating into favourable long-term OS.

Whilst OS is generally considered to be the most reliable and patient relevant endpoint in oncology, PFS data have previously been used to support regulatory approvals in mCRC, particularly when the magnitude of PFS benefit is expected to be substantial.[131,132] Specifically, the FDA have accepted PFS as a surrogate marker for OS when issuing approvals across a range of solid tumours, including CRC. In addition, the FDA have ruled that this surrogate relationship may be considered mechanism agnostic, where the relationship has been validated for treatments with a range of mechanisms of action; therefore, not directly related to a particular causal pathway.[133]

In a *post-hoc* analysis, the patient-level association between PFS and OS in CM142 was assessed, showing a strong rank association across multiple models; the range of estimates for Spearman's rho were 0.82–0.95, with an estimate from the chosen copula model of 0.92, where a score of 1 represents perfect rank correlation.[123] Regulatory authorities have typically required verification of a predictive level, both at the individual and trial level.[134] The German Institute for Quality and Efficiency in Health Care (IQWIG), provides guidelines for interpreting the R value for statistical

association (corresponding to the correlation coefficient; in this case, Spearman's Rho), indicating cut-offs where surrogates are deemed suitable for regulatory use. IQWIG considers that surrogates have an unclear relationship when the R-value is >0.7 and < 0.85; surrogate measures are considered to have proven validity when the R-value is ≥ 0.85.[135] This guidance supports the strong relationship between PFS and OS demonstrated from the CM142 analysis, inferring that the PFS benefits observed in CM8HW are likely to translate into long-term OS benefits and that PFS may be considered as an appropriate surrogate endpoint for OS in this population.

PEMBRO is another IO recently approved for the treatment of patients with previously untreated dMMR/MSI-H mCRC;[1] however, this drug has limitations, including the high number of patients with a best response of PD (29.4%) in KN-177, leading to a low initial plateau (PFS rate 55.3% at 12 months), with a median PFS of 16.5 months. By contrast, the PFS curve for NIVO + IPI in the centrally confirmed population in CM8HW demonstrated a high plateau and sustained benefit, with a 12-month PFS rate of 78.7% and median PFS not reached. Across multiple ITC approaches, NIVO + IPI demonstrated significant PFS benefits over PEMBRO, which was apparent by 12 months and maintained at 60 months.

Additionally, NIVO + IPI demonstrated PFS benefits across subgroups in CM8HW (Section B.2.5.1); however, in KN-177, the HR for PFS did not favour PEMBRO in those aged > 70, people with an ECOG PS of 1, people with left-sided tumours, and people with KRAS or NRAS mutations.[1,69]

NIVO + IPI demonstrated a risk-benefit profile aligned with expectations for the class, and consistent with the safety profile observed for NIVO + IPI in other indications.[136] The safety profile was favourable compared with chemotherapy; in CM8HW, grade 3-4 TRAEs occurring in [redacted] patients in the NIVO + IPI arm and [redacted] patients in the chemotherapy arm. No grade 3 or 4 IMAEs occurred in ≥5% of participants; the majority of immune-mediated AEs were resolved and were manageable with standard treatment. Similarly, there were no significant differences between NIVO + IPI and PEMBRO, with the exception of treatment-related adverse events of grade ≥3 where NIVO + IPI had a higher odds ratio.

In addition, CM142 provided long-term safety data. No new safety signals were identified at 64 months of follow-up. Most AEs were grade 1–2, with grade 3–4 TRAEs occurring in 9 (20%) patients. The majority of immune-mediated AEs resolved, and were manageable with standard treatment.[121] Safety data are consistent with long term observations (median 7.5 year follow up) in renal cell carcinoma, where NIVO+IPI with dosing aligned to CM8HW showed favourable safety profile compared to chemotherapy.[137]

In dMMR/MSI-H mCRC patients, chemotherapy is associated with reduced QoL, which may be due to a combination of characteristic adverse events and the reduced chemosensitivity of MSI-H tumours.[107,108] In CM8HW, NIVO + IPI was associated with sustained improvements in EQ-5D-3L utility scores, reaching the MCID at several timepoints over 101 weeks of follow-up; the chemotherapy arm, however, showed a trend towards decreased utility scores, supporting an approach with treatment specific utilities in the cost effectiveness model.

B.2.10.2 Strengths and limitations of the clinical evidence

Clinical efficacy data for NIVO + IPI are derived from the phase 3 CM8HW study and supported by phase 2 CM142. Whilst the studies are robust, the following section discusses their limitations, none of which affect generalisability to the UK population and should be viewed within the context of each study's strengths and the high unmet need in this patient population:

- **Open label study design**: the open-label study design of CM142 and CM8HW means that it is possible that patient-reported outcomes could have been influenced by knowledge of the treatment; however, the open-label design should not affect the key efficacy endpoints, which are objective measures (PFS, ORR, OS). Further, an open-label design was considered appropriate due to differences in the dosing regimens and associated toxicities across study treatments, facilitating optimal safety assessment. It is also to be noted that CM142 was considered appropriate primary evidence for the appraisal of NIVO + IPI in the 2L dMMR/MSI-H mCRC population, in TA716.[74]

- **Lack of mature survival data in CM8HW**: mature OS data are not available for CM8HW, which is ongoing. However, evidence from CM142 shows that NIVO + IPI is associated with sustained survival benefits with PFS and OS not reached after 64.2 months of follow-up; in addition, a strong association between PFS and OS in this cohort has been demonstrated, providing support for the use of PFS as a surrogate endpoint for OS in the absence of mature survival data.[123] This is further supported by a meta-analysis of 40 randomised trials investigating PD-1/PD-L1 targeting immunotherapies, which also found a strong correlation between PFS and OS in the 1L setting (rho = 0.84), concluding that improvements in PFS are likely to translate into OS benefits.[138] Additionally, it is common in IO appraisals in dMMR/MSI-H mCRC that median OS is not reached, as in TA716 (NIVO + IPI in previously-treated dMMR/MSI-H mCRC) and TA709 (PEMBRO in previously untreated dMMR/MSI-H mCRC);[1,74] in TA716, it was considered that awaiting OS data would necessitate significant delay in patients being able to access a treatment which would fulfil an unmet need, and which had demonstrated efficacy.[74] This has also been the case in appraisals of NIVO + IPI in other indications, such as for the treatment of advanced melanoma (TA400).[136] In previous NIVO appraisals in the adjuvant setting, disease-free survival (DFS) has also been considered as a suitable surrogate endpoint for OS (TA817, TA746), in the absence of OS or response data.[139,140]

- **Absence of direct trial-based comparison between NIVO + IPI and PEMBRO:** this limitation has been addressed via an ITC, which compares NIVO + IPI with PEMBRO by matching the common chemotherapy arms in CM8HW and KEYNOTE-177 (KN- 177). Across all ITC approaches (anchored and unanchored MAIC, FP NMA, constant hazard NMA), there was a clear and consistent PFS benefit for NIVO + IPI over PEMBRO.

- **Inclusion of chemotherapy regimens not relevant in the UK**: CM8HW was not conducted exclusively in the UK, and therefore, the chemotherapy arm included concomitant treatment with some regimens which, whilst commonly used in other countries, are not part of UK standard practice. Additionally,

there are some regimens commonly used in UK clinical practice which are not included in CM8HW.

- **Bevacizumab:** bevacizumab-containing regimens are no longer used in UK clinical practice;[141] however, we may reasonably assume that bevacizumab-containing regimens have efficacy analogous to cetuximab-containing regimens, and that they are more clinically effective than FOLFOX or FOLFIRI alone, as was considered appropriate in TA709 appraisal of PEMBRO.[1] This assumption is considered conservative, since bevacizumab has been associated with longer OS compared with cetuximab.[1,95] The *post-hoc* subgroup analysis of CM8HW chemotherapy cohorts (Section B.2.5.1.1) supported this conclusion, demonstrating that median PFS in bevacizumab-treated patients is substantially greater than PFS in patients treated with cetuximab or FOLFOX/FOLFIRI alone. As a result, the NIVO+IPI vs. SoC chemotherapy comparison from CM8HW ITT population would represent an underestimate of the relative efficacy of NIVO+IPI compared to a NIVO+IPI versus FOLFOX/FOLFIRI alone comparison. It should also be noted that [redacted] treated with bevacizumab in CM8HW were BRAF/KRAS/NRAS wildtype so would be expected to receive cetuximab or panitumumab in UK clinical practice. Therefore, we can expect efficacy results for CM8HW to further overestimate chemotherapy treated patient outcomes compared to what would be expected in UK clinical practice, supporting the argument that it is conservative to consider the CM8HW chemotherapy ITT population as the primary source of evidence in this appraisal.

- **CAPOX**: this regimen is not included in CM8HW, but is used in UK clinical practice.[1] However, it may be assumed that FOLFIX, FOLFIRI and CAPOX have comparable efficacy, as in TA709.[1] This is based on clinical trial evidence which demonstrates that CAPOX and FOLFIRI are similar with respect to PFS (or TTP) and OS,[142-145] and FOLFOX and FOLFIRI are similar with respect to OS, TTP and ORR. [146]

- **Panitumumab:** panitumumab-containing regimens are not included in CM8HW, but are used in UK clinical practice.[147] However, cetuximab-containing regimens are included, and it may be assumed that panitumumab and cetuximab have comparable efficacy, as concluded during TA709.[1] This is based on an NMA presented in TA439, for panitumumab plus cetuximab in 1L treatment of mCRC, which showed that there were no significant differences in PFS and OS between FOLFOX + cetuximab and FOLFOX + panitumumab.[147]

- **Difference in dosing schedule between CM8HW and CM142:** in CM8HW, ipilimumab was administered for four cycles only according to the protocol, leading to a median treatment duration of 2.1 months (13.5 months for nivolumab). This dosing schedule is in line with the NIVO+IPI SmPC and considered the most relevant dosing schedule in the UK and for this appraisal. In CM142, there was no such restriction on number of doses, leading to a median treatment duration of 18.1 months for ipilimumab (19.1 months for nivolumab). This may lead to uncertainty regarding the durability of response observed in the CM142 trial; however, [redacted] of all participants in CM142 had discontinued study treatment at 36 months, with 72% of participants still in response at 60 months and PFS/OS not reached. This demonstrates that survival benefits of NIVO + IPI may be expected to continue beyond the point of discontinuation; further, both trials demonstrate similar long-term PFS outcomes, with 36-month PFS rates of 64% and 60% for CM8HW and CM142 respectively.[120,121] Additionally, across CM142 cohort 1 (2L+ NIVO monotherapy) and cohort 2 (2L+ NIVO + IPI), NIVO + IPI demonstrated (improvements over NIVO monotherapy in terms of 5-year PFS and OS, using a similar IPI dose schedule to CM8HW (IPI only given for four doses Q3W). Similar outcomes have been demonstrated in real world evidence comparing NIVO + IPI with immunotherapy monotherapy in other indications, as well as indirect comparisons.[85,86] Hence, it may be expected that the synergistic action of NIVO + IPI leads to improved outcomes relative to anti-PD-1 monotherapy, even after dual therapy is discontinued.[84]

- **Lack of adolescent patients in CM8HW and CM142:** only adult patients were recruited for CM8HW and CM142. However, a pharmacokinetic simulation study concluded that the exposure of the proposed dosing regimen for both NIVO and IPI in adolescents is expected to result in comparable benefits and risks to those in adults.

Strengths of the trials include:

- **Robust study design**: both CM142 and CM8HW were well-designed, high-quality, randomised trials. In CM142, 59 1L patients were randomised to NIVO + IPI; in CM8HW, 202 patients were randomised. In both cases, the study design is statistically rigorous, with appropriate sample size and power, multiplicity-controlled endpoints, and length of follow-up which allows for the rigorous evaluation of efficacy and safety data.

- **Maturity of survival data in CM142**: median follow-up in CM142 was 64.2 months. These data therefore provide evidence of long-term treatment effects, with follow-up more extensive than any previous IO study considered as evidence during appraisal for mCRC. In the interim analysis for CM8HW, median follow-up (min, max) from randomisation until clinical cutoff date in the centrally confirmed population was 31.57 (6.1, 48.4) months, and median follow-up until death or last known date alive was 24.28 (0, 48.4) months.

- **Primary endpoint met in CM8HW:** in CM8HW, the primary endpoint was met, demonstrating a clinically meaningful and statistically significant improvement in PFS in patients receiving NIVO + IPI compared with chemotherapy (HR by Cox model: 0.21 (0.14, 0.32); HR by max combo test: [redacted]), both p<0.0001).

- **Thorough characterisation of safety profile**: in CM8HW, select AEs and IMAEs were recorded. Although grade 3 or 4 IMAEs are rare (<5%) and have gone unaddressed in previous mCRC submissions, they are of particular importance to clinicians as they can result in life-threatening complications, and combination therapies have the potential for novel toxicities.[148] In

CM8HW, most IMAEs that arose were effectively managed, with only one death reported due to pneumonitis.

- **Relevant patient populatio**n: in CM142, the majority of randomised patients were European, and in CM8HW, the majority were either European or North American. In addition, dMMR/MSI-H assessment was conducted in accordance with UK clinical practice:[23] in CM8HW, dMMR/MSI-H tumours were confirmed through central testing, employing either an IHC panel that tested for the absence of MLH1, MSH2, MSH6 and PMS2 expression, or an MSI test that detected mutations at specific MSI loci.[114] Thus, the CM8HW trial protocol is aligned with UK recommendations for dMMR/MSI-H.

    - **Similarity of KN-177 and CM8HW populations:** In TA709, the evidence review group's (ERG) clinical experts concluded that the characteristics of the KN-177 population were representative of the population with dMMR/MSI-H mCRC who were likely to be eligible for PEMBRO in England.[1] The patient population in CM8HW is broadly similar to that in KN-177, with a median age of 63.0 years in both CM8HW and KN-177, and similar proportions of patients having an ECOG PS of 1 (46.2% and 48.2% respectively). The populations were also similar with regard to the prevalence of characteristics identified in the literature as negative prognostic factors, including tumour right-sidedness (68.0% vs. 68.1%),[112] and BRAF mutations (25.1% vs. 24.1%).[149,150] The metastatic pattern was relatively similar across trials and potentially elevated in CM8HW compared to KN-177, indicating a population with worse prognosis;[99-101] 38.9% of patients in CM8HW had liver metastases and 22.8% had lung metastases, whilst in KN-177, 51.8% had liver or lung metastases and 40.7% had liver metastases. The percentage of patients with peritoneal metastases in CM8HW was 41.9%; whilst this is not reported for KN-177; however, in real-world UK populations, the prevalence of peritoneal metastases may be < 25%, indicating a potentially worse prognosis in CM8HW than would be expected in the relevant UK mCRC population.[2,151] In addition, the chemotherapy populations in both trials are similar,

including a similar proportion of patients receiving bevacizumab (64% in CM8HW and 70% in KN-177).[1,69,118] Overall it may be considered that the populations of CM8HW and KN-177 are comparable, and thus, CM8HW population is representative of the dMMR/MSI-H mCRC population in England being considered in this appraisal.

- **Relevance of the evidence base to the decision problem:** The submission presents evidence from the CM8HW and CM142 studies, which studied the safety and efficacy of NIVO + IPI in untreated patients with mCRC with MSI-H and dMMR, in line with the decision problem. However, there were some differences in comparator treatments evaluated. In line with TA709, capecitabine was not considered a relevant comparator, as it is generally used in elderly patients with poor ECOG PS.[1] In addition, direct comparisons between NIVO + IPI and CAPOX, as well as panitumumab-containing regiments, were not available; however, comparable efficacy may be assumed between CAPOX and FOLFOX/FOLFIRI, and between panitumumab and cetuximab. [142-147]

B.2.10.3 External validity of study results to patients in routine clinical practice

In CM8HW, the majority of patients were from the US/Canada/Europe region, with subgroup analysis demonstrating that the PFS benefits of NIVO + IPI spanned study regions (Section B.2.5.1). Whilst non-UK study sites were included, patient characteristics in CM8HW are well aligned to those in KN-177 (Section B.2.10.2), which has previously been considered representative of the eligible dMMR/MSI-H mCRC population in England under consideration in this appraisal.[1]

The inclusion of non-UK study sites introduced treatment regimens which are not used in UK clinical practice; however, a *post-hoc* subgroup analysis demonstrated that bevacizumab-treated patients had substantially greater median PFS than those treated with other regimens; thus, consideration of CM8HW ITT population as the primary source of efficacy in this appraisal introduces bias that favours SoC chemotherapy and may underestimate the true PFS for NIVO+IPI versus chemotherapy regimens routinely used in UK clinical

practice. This conclusion and consideration that the bevacizumab containing ITT population is appropriate for appraisal of previously untreated mCRC aligns with the EAG and clinical expert opinion from TA709.[1]

In addition, the CM8HW population was aligned with UK guidelines for dMMR/MSI-H assessment.[23] In CM8HW, dMMR/MSI-H tumours were confirmed through central testing, employing either an IHC panel that tested for the absence of MLH1, MSH2, MSH6 and PMS2 expression, or an MSI test that detected mutations at specific MSI loci.[114]

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

In line with the NICE requirements, an SLR was conducted to identify cost-effectiveness studies for the treatment of mCRC. A full description of SLR methodology and outcomes is provided in Appendix G. A brief overview is provided below.

In brief, electronic database searches (MEDLINE, Embase and EconLit) were searched from inception to 29 July 2021, and subsequently updated on 17 May 2024. Publications describing full economic evaluations of interventions aimed at managing mCRC were included. Outcomes from the SLR are provided in Table 49, while the study flow is provided in Figure 30.

Table 49. Summary list of published cost-effectiveness studies

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
Records identified by SLR conducted 2021 to 2024 (n =13)									
NICE TA866 [Regorafenib], 2022[152] UK	Regorafenib, trifluridine/ tipiracil and BSC	GBP (2021)	Censored	Censored	Censored	Censored	Censored	Censored (Regorafenib is a cost effective alternative to BSC in mCRC)	The model evaluates regorafenib, trifluridine/ tipiracil and BSC for mCRC treatment. The analysis is conducted from UK NHS and PSS perspective using a de novo partitioned survival (area under the curve) model for 10 years' time horizon with 3.5% discount rate. Sensitivity and scenario analysis was performed.
NICE TA716 [Nivolumab + ipilimumab], 2021[153]	Nivolumab + ipilimumab (Company's base-case results with PAS)	GBP (2018-19)	Censored	Censored	NR	Censored	NR	Reference	The model evaluates nivolumab + ipilimumab as third-line treatment. The analysis is conducted from NHS Healthcare payer perspective using a partitioned survival model for Lifetime (up to 50 years or
	Trifluridine/ tipiracil (Company's base-case results with PAS)		16,978	Undiscounted: 0.915	NR	0.63	NR	13,367	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	BSC (Company's base-case results with PAS)		9,379	Undiscounted: 0.639	NR	0.441	NR	14,211	2,609 weeks) horizon with 3.5% discount rate. Scenario analysis, PSA And DSA was performed.
	FOLFIRI (Company's base-case results with PAS)		12,176	Undiscounted: 1.314	NR	0.884	NR	14,839	
	FOLFOX (Company's base-case results with PAS)		11,527	Undiscounted: 1.284	NR	0.874	NR	14,930	
	Irinotecan (Company's base-case results with PAS)		11,139	Undiscounted: 1.295	NR	0.883	NR	15,022	
	Raltitrexed (Company's base-case results with PAS)		13,389	Undiscounted: 1.71	NR	1.147	NR	15,346	
	BSC (ERG's base case results)		9,303	NR	NR	0.376	NR	Reference	
	FOLFIRI (ERG's base case results)		11,525	NR	NR	0.822	NR	4,982	
	FOLFOX (ERG's base case results)		12,334	NR	NR	0.877	NR	14,709	
	Nivolumab + ipilimumab (ERG's base case results)		Censored	NR	NR	Censored	NR	40,976	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	Nivolumab + ipilimumab (Company's revised base case results)		Censored	Censored	NR	Censored	NR	Reference	
	Trifluridine/ tipiracil (Company's revised base case results)		17,020	1	NR	0.689	NR	15,743	
	BSC (Company's revised base case results)		9,546	0.691	NR	0.477	NR	16,323	
	FOLFOX (Company's revised base case results)		12,564	1.546	NR	1.029	NR	17,220	
	FOLFIRI (Company's revised base case results)		12,289	1.931	NR	1.287	NR	17,981	
NICE TA709 [Pembrolizumab], 2021[154] UK	Pembrolizumab	GBP (2018/ 2019)	NR	NR	NR	4.24	NR	7,250 vs BSC 27,480 vs CAPOX	The model evaluates pembrolizumab as a first-line treatment. The analysis is conducted from the UK NHS and PSS perspective using a semi-Markov model with a cycle length of one-week, half-cycle correction applied, and a lifetime
	SOC		NR	NR	NR	2.38	NR	Reference	
	CAPOX		NR	NR	NR	2.39	NR	Reference	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
									horizon (40 years) with a 3.5% discount rate. Deterministic, probabilistic, and scenario analysis was performed.
NICE TA668 [Encorafenib + Cetuximab] 2020[155] UK	ENCO + CET FOLFIRI	GBP (NR)	Censored	1.36	NR	0.92	NR	Censored	The model evaluates ENCO + CET in pre-treated patients setting. The analysis is conducted from NHS and PSS Healthcare payer perspective using a partitioned survival model for 10 years (lifetime) time horizon with 3.5% discount rate. Scenario analysis, PSA And DSA were performed.
	FOLFIRI		12,434	0.59	NR	0.40	NR	NA	
	Trifluridine/ tipiracil		Censored	0.38	NR	0.26	NR	Dominated	
NICE TA439 [Cetuximab and Panitumumab], 2017[156]	PenTAG: CET+FOLFOX vs FOLFOX	GBP (2015/16)	Mean discounted: 73,639	Mean undiscounted: 2.41	NR	Mean discounted: 1.61	NR	123,000	The model evaluates cetuximab and Panitumumab in previously untreated, RAS wild-type mCRC patients setting. The analysis is conducted from NHS and PSS Healthcare payer perspective using
	PenTAG: PAN+FOLFOX vs FOLFOX		Mean discounted: 64,177	Mean undiscounted: 2.08	NR	Mean discounted: 1.41	NR	224,000	
	PenTAG: FOLFOX		Mean discounted: 30,585	Mean undiscounted: 1.86	NR	Mean discounted: 1.26	NR	Reference	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	PenTAG: CET+FOLFIRI vs FOLFIRI		Mean discounted: 80,018	Mean undiscounted: 2.21	NR	Mean discounted: 1.53	NR	166,000	Markov model for 10 years and 30 years' time horizon for Merck Serono and PenTAG models respectively with 3.5% discount rate. Scenario analysis, PSA and DSA were performed.
	PenTAG: FOLFIRI		Mean discounted: 29,668	Mean undiscounted: 1.75	NR	Mean discounted: 1.23	NR	Reference	
	Merck Serono: CET+FOLFOX vs FOLFOX		41,301	2.22	NR	1.64	36,048	46,503	
	Merck Serono: FOLFOX		26,408	1.81	NR	1.32	Reference	Reference	
	Merck Serono: CET+FOLFIRI vs FOLFIRI		43,592	2.19	NR	1.61	42,990	55,971	
	Merck Serono: FOLFIRI		27,139	1.81	NR	1.32	Reference	Reference	
	Merck Serono: CET+FOLFIRI		37,978	2.16	NR	1.60	24,191	32,726	
	Merck Serono: BEV+ FOLFIRI		34,605	2.03	NR	1.49	Reference	Reference	
NICE TA405 [Trifluridine with tipiracil hydrochloride], 2016[157] UK	BSC: Company's base-case results including PAS	GBP (NR)	10,286	0.66	Pre-progression: 0.16 Post-progression: 0.50	Pre-progression: 0.12 Post-progression: 0.30 Total: 0.42	NR	Reference	The model evaluates trifluridine/ tipiracil as third-line treatment. The analysis is conducted from NHS Healthcare payer perspective using a

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	BSC: RECOURSE, ERG's base-case results including PAS		9,605	NR	NR	0.40	NR	Reference	partitioned survival model for 10 years horizon with censored† discount rate. Scenario analysis, PSA And DSA was performed.
	BSC: Pooled analysis, ERG's base-case results including PAS		9,584	NR	NR	0.407	NR	Reference	
	Trifluridine/ tipiracil: Company's base-case results including PAS		16,386	0.92	Pre-progression: 0.30 Post-progression: 0.62	Pre-progression: 0.22 Post-progression: 0.37 Total: 0.59	NR	44,032 vs BSC (Base case)	
	Trifluridine/ tipiracil: RECOURSE, ERG's base-case results including PAS		17,167	NR	NR	0.54	NR	52,695	
	Trifluridine/ tipiracil: Pooled analysis, ERG's base-case results including PAS		17,197	NR	NR	0.561	NR	49,392 vs BSC pooled analysis	
	Trifluridine/ tipiracil: Budget impact analysis		1st year annual cost Total: 3,148,337	NR	NR	NR	NR	NR	At the PAS price, the total budget impact of trifluridine/tipiracil in the first year of availability would be

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
			Drug only: 3,189,673 2nd year annual cost Total: 6,465,953 Drug only: 5,120,158 3rd year annual cost Total: 9,401,427 Drug only: 6,952,320 4th year annual cost Total: 10,302,300 Drug only: 7,064,941 5th year annual cost Total: 10,668,729 Drug only: 7,108,245						expected to be approximately £3.15 million, rising to £10.67 million in Year 5.

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
SMC 2589 [Pembrolizumab], 2024[158] UK	Pembrolizumab	GBP (2020-2021)	NR	NR	NR	NR	NR	Reference	The model evaluates the use of pembrolizumab. The analysis is conducted from NHS perspective using partitioned survival model for lifetime (40 years) horizon. Scenario analysis was performed.
	Trifluridine/ tipiracil, FOLFIRI/FOLFOX regimens		NR	NR	NR	NR	NR	39,372	
SMC 2562 [Regorafenib], 2023[159] UK	Budget impact analysis for regorafenib (Year1, n=518 Year5, n=525)	GBP (NR)	Censored	NR	NR	NR	NR	NR	The submitting company estimated there would be 518 patients eligible for treatment with regorafenib in year 1, rising to 525 patients in year 5 to which confidential uptake rates were applied. SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
									template does not incorporate any PAS discounts associated with comparator medicines.
SMC 2312 [Encorafenib + cetuximab] 2021[160] UK	Encorafenib + cetuximab	GBP (NR)	67,482	1.46	NR	0.98	NR	Reference	The model compared encorafenib plus cetuximab for the second- or third-line treatment. The analysis is conducted from NHS perspective using partitioned survival cohort simulation model for 10-year time horizon. Scenario analysis was performed.
	FOLFIRI		12,388	0.6	NR	0.41	NR	96,448	
	Trifluridine-tipiracil		14,782	0.38	NR	0.26	NR	72,914	
SMC 2394 [Nivolumab], 2021[161] UK	Nivolumab + ipilimumab (Base case results with PAS)	GBP (NR)	NR	NR	NR	NR	NR	Reference	The model evaluates the use of nivolumab in combination with ipilimumab. The analysis is conducted from the UK NHS perspective using a partitioned survival model with a cycle length of one week, and a time horizon of 50 years. Scenario analysis was performed.
	BSC (Base case results with PAS)		NR	NR	NR	NR	NR	16,456	
	FOLFOX (Base case results with PAS)		NR	NR	NR	NR	NR	17,184	
	FOLFIRI (Base case results with PAS)		NR	NR	NR	NR	NR	17,973	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	Trifluridine/ tipiracil, FOLFIRI/FOLFOX regimens		NR	NR	NR	NR	NR	39,372	
SMC 1221/17 [Trifluridine/ tipiracil], 2017[162] UK	Trifluridine/ Tipiracil	GBP (NR)	NR	NR	0.27	NR	NR	49,225	The model evaluates the use of trifluridine/ tipiracil. The analysis is conducted from the UK NHS perspective using a Partitioned survival model with a daily cycle and a time horizon of 10 years.
	BSC		NR	NR		NR	NR	Reference	
	Budget impact analysis for Trifluridine/ tipiracil (Year 1, n=204 Year 5, n=211)		Censored	NR	NR	NR	NR	NR	The submitting company estimated there would be 204 patients eligible for treatment with trifluridine/ tipiracil in year 1, rising to 211 patients in year 5. The estimated uptake rate was 15% in year 1 (31 patients), rising to 30% in year 5 (63 patients) based on clinical expert opinion obtained by the submitting company is unable to publish the with PAS budget impact due to commercial in

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
									confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.
SMC 878/13 [Aflibercept], 2014[163] UK	Aflibercept + FOLFIRI (base case results with PAS)	GBP (NR)	NR	NR	NR	NR	NR	34,623	The model evaluates the use of aflibercept plus FOLFIRI to FOLFIRI alone. The analysis is conducted from the UK NHS perspective using a Markov model with a time horizon of 15 years. Scenario analysis was also performed.
	FOLFIRI (base case results with PAS)		NR	NR	NR	NR	NR	Reference	
	Budget impact analysis for Aflibercept (N=286)		1st year annual cost Gross impact: 350,000 Net medicine budget impact: 350,000 5th year annual cost	NR	NR	NR	NR	NR	Without PAS, the gross impact on the medicines budget was estimated to be £350k in year 1 and £1.373m in year 5. As no other drugs were assumed to be displaced, the net medicines budget impact is expected to remain as £350k in year 1 and £1.373m in year 5.

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
			Gross impact: 1,372,000 Net medicine budget impact: 1,372,000						
Henderson (2022)[164]	Intermittent cetuximab	GBP (2013) GBP (2013)	53, 334	NR	NR	1.1255	NR	NR	The analysis is conducted from NHS perspective using Markov model for 6-year time horizon with weekly cycle.
	Continuous cetuximab		83, 523	NR	NR	1.2297	NR	NR	
	Intermittent cetuximab		70, 168	NR	NR	1.2573	NR	NR	The analysis is conducted from NHS perspective using partitioned survival model for lifetime horizon
	Continuous cetuximab		105, 931	NR	NR	1.2465	NR	NR	
Records identified by SLR conducted from database inception to 2021									
Bullement (2018)[165] UK	Trifluridine/ tipiracil	GBP (NR)	17,978.00	0.92	NR	0.57	NR	51,194.00 vs BSC	The model evaluates trifluridine/tipiracil for previously treated patients with mCRC. The analysis is conducted from a payer perspective using a Partitioned survival model for 10 years-time horizon with 3.5% discount rate.
	Regorafenib		24,112.00	0.82	NR	0.51	NR	1,33,561.00 vs BSC	
	BSC		9,499.00	0.66	NR	0.40	NR	Reference	
	Regorafenib vs trifluridine/ tipiracil		NR	NR	NR	NR	NR	Trifluridine/ tipiracil dominates	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
Tikhonova (2018)[166] UK	CET + FOLFOX	GBP (2015/16)	Mean discounted: 62,436	Mean undiscounted: 2.52	NR	Mean discounted: 1.67	NR	243,975	The model evaluates cetuximab and panitumumab in previously untreated, RAS wild-type mCRC patients setting. The analysis is conducted from NHS and PSS perspective using partitioned survival model for 30 years time horizon with 3.5% discount rate. Scenario analysis was performed.
	FOLFOX		Mean discounted: 32,729	Mean undiscounted: 2.35	NR	Mean discounted: 1.55	NR	Reference	
	PAN + FOLFOX		Mean discounted: 65,526	Mean undiscounted: 2.85	NR	Mean discounted: 1.86	NR	106,276	
	FOLFOX		Mean discounted: 32,729	Mean undiscounted: 2.35	NR	Mean discounted: 1.55	NR	Reference	
	CET + FOLFIRI		Mean discounted: 70,543	Mean undiscounted: 2.9	NR	Mean discounted: 1.92	NR	83,168	
	FOLFIRI		Mean discounted: 29,596	Mean undiscounted: 2.1	NR	Mean discounted: 1.43	NR	Reference	
Goldstein (2017)[167] UK	FOLFOX	USD (2016)	NR	NR	NR	NR	Reference	Reference	The model compares bevacizumab + FOLFOX to FOLFOX alone as a first-line treatment. The analysis is conducted from a payer perspective using a Markov model. However, discount rate and time horizon were not reported.
	Bevacizumab + FOLFOX		NR	NR	NR	NR	270,941	352,734	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
Hoyle (2013)[168] UK	BSC	GBP (2011-2012)	Mean discounted: 6,256	Undiscounted Mean: 1.51 Median: 1.40	Undiscounted Time on drug treatment: NA Progression free: 0.23 Post progression: 0.29	Mean discounted Progression free: 0.17 Post progression: 0.19 Total: 0.36	Reference	Reference	The model evaluates cetuximab monotherapy, cetuximab plus irinotecan, and panitumumab monotherapy as third and subsequent lines of treatment. The analysis is conducted from NHS and Personal Social Services perspective using an area under the curve/partitioned survival Markov-type model for 10 years' time horizon with 3.5% discount rate.
	Cetuximab		Mean discounted: 28,860	Undiscounted Mean: 0.84 Median: 0.75	Undiscounted Time on drug treatment: 0.36 Progression free: 0.40 Post progression: 0.44	Mean discounted Progression free: 0.31 Post progression: 0.29 Total: 0.60	72,000	95,000	
	Panitumumab		Mean discounted: 35,213	Undiscounted Mean: 0.71 Median: 0.60	Undiscounted Time on drug treatment: 0.49 Progression free: 0.42 Post progression: 0.29	Mean discounted Progression free: 0.33 Post progression: 0.19 Total: 0.52	153,000	187,000	

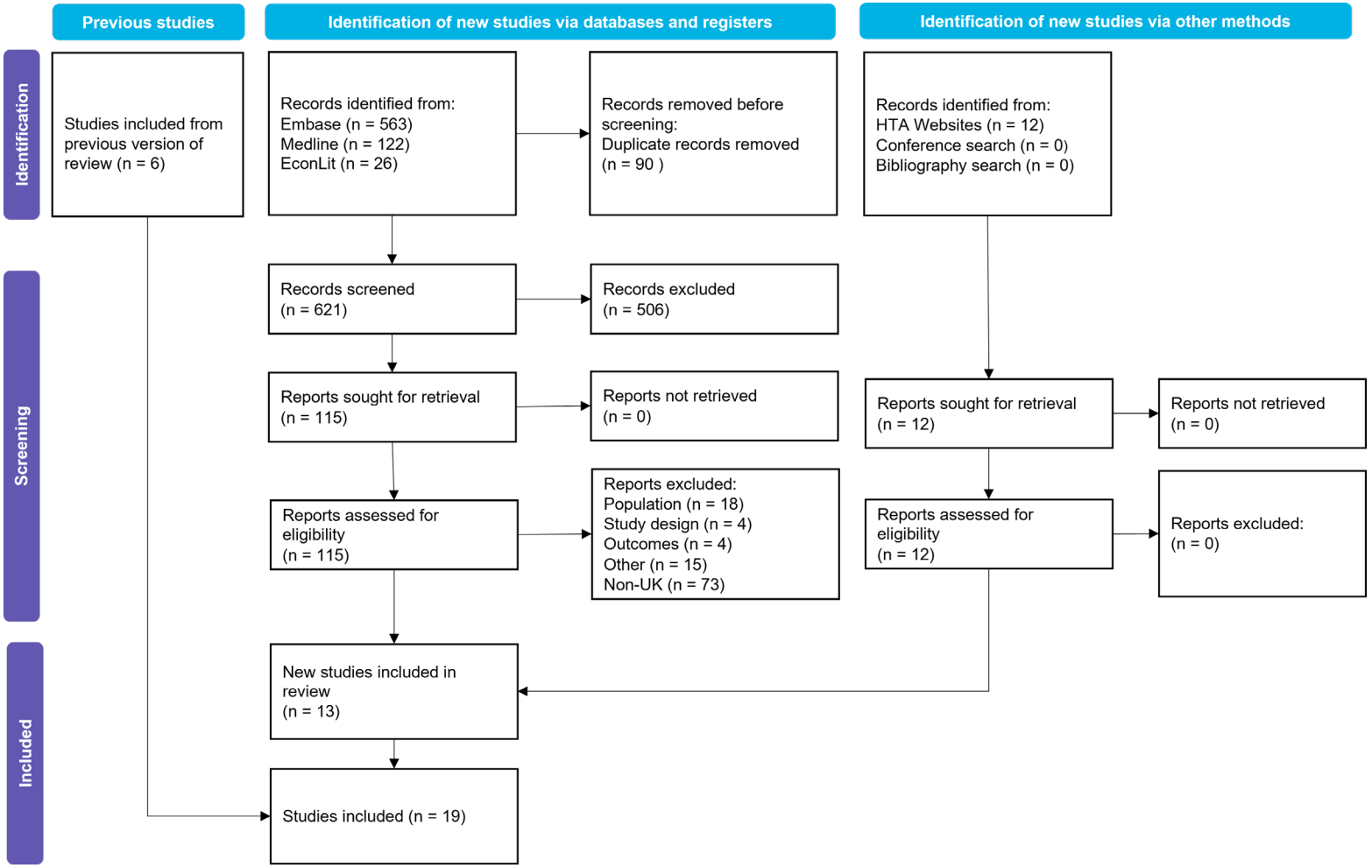
Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	Cetuximab + irinotecan		Mean discounted: 59,348	Undiscounted Mean: 1.38 Median: 1.25	Undiscounted Time on drug treatment: 0.73 Progression free: 0.73 Post progression: 0.65	Mean discounted Progression free: 0.54 Post progression: 0.43 Total: 0.97	64,000	88,000	
Tappenden (2007)[169] UK	Bevacizumab + Irinotecan + FU/LV (Study AVF2107g)	GBP (2005)	43,140	1.98	NR	1.44	46,853	62,857	The model estimates the marginal cost-effectiveness of two bevacizumab-containing chemotherapy regimens for the first-line treatment of mCRC. The analysis is conducted from the UK Payer's perspective using a Decision-analytic model with a lifetime time horizon.
	Irinotecan + FU/LV + placebo (Study AVF2107g)		23,779	1.57	NR	1.13	Reference	Reference	
	Bevacizumab + 5-FU/LV (Study AVF2192g)		37,074	1.59	NR	1.19	84,396	88,436	
	5-FU/LV (Study AVF2192g)		21,459	1.41	NR	1.01	Reference	Reference	
Iveson (1999)[170] UK	Irinotecan	GBP (1996/1997)	8,253	0.9 (Survival)	NR	NR	Reference	NR	The analysis is conducted from Purchaser in the

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	De Gramont regimen, B1†		6,791	0.7 (Survival)	NR	NR	7,695 (incremental cost/survival)	NR	NHS perspective. Scenario analysis was performed.
	Lokich regimen, B2‡		5,983	0.7 (Survival)	NR	NR	11,947 (incremental cost/survival)	NR	
	B3§a (50% of patients receive the treatment as an inpatient)		9,981	0.7 (Survival)	NR	NR	Dominated (incremental cost/survival)	NR	
	B3§b (50% receive the treatment as 1-day hospital attendance)		8,958	0.7 (Survival)	NR	NR	Dominated (incremental cost/survival)	NR	

Note: †B1, Folinic acid 200 mg/m^2 + 5-FU 400 mg/m^2 + 5-FU 600 mg/m^2; ‡B2, 5-FU 250-300 mg/m^2; §B3, 5-FU 2600-3000 mg/m2 + folinic acid 20±500 mg/m^2.

Abbreviations: UK, united kingdom; NHS, national health service; PSS, personal social services; mCRC, metastatic colorectal cancer; BSC, best supportive care; FOLFIRI, folinic acid (leucovorin/levo-leucovorin) + 5-fluorouracil + irinotecan; FOLFOX, folinic acid, 200mg (leucovorin/levo-leucovorin) + 5-fluorouracil + oxaliplatin; CAPOX, XELOX, oxaliplatin + capecitabine; mFOLFOX6,modified version of folfox4; SOC, standard of care; ENCO, encorafenib; CET, cetuximab; BI, budget impact; 5-FU,5-fluorouracil; LV, leucovorin; NICE, national institute for health and care excellence; TA, technology appraisal ; SMC, Scottish medicines consortium; GBP, great British pound; QALY, quality adjusted life year; PSA, probabilistic sensitivity analysis; DSA, deterministic sensitivity analysis; PAS, patient access scheme; ERG, evidence review groups; NR, not reported.

Figure 30. PRISMA diagram illustrating the study selection process for identifying cost effectiveness studies



B.3.2 Economic analysis

The economic case presented in this submission is based on a conventional cost-utility analysis, assessing use of nivolumab plus ipilimumab (NIVO + IPI) for the treatment of previously untreated patients aged 12 years and over with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC), taking into account a simple discount patient access scheme (PAS). Pembrolizumab (PEMBRO) is considered as a key comparator, as it is the only therapy specifically recommended for untreated dMMR/MSI-H mCRC,[1] with additional comparisons versus chemotherapy (FOLFOX, FOLFIRI, CAPOX, cetuximab with FOLFOX or FOLFIRI, panitumumab with FOLFOX or FOLFIRI, capecitabine monotherapy and FOLFOXIRI). The analysis includes simple discount patient access schemes (PAS) for NIVO and IPI.

A semi-Markov model approach has been utilised, which is more suitable when overall survival (OS) data is immature and when external data is used to inform time-to-event data such as post-progression survival (PPS). This approach is aligned with that in previous NICE technology appraisals (TAs), TA709 and TA439, both of which incorporated a semi-Markov model structure.[1,71] The use of a semi-Markov approach was the preference of the evidence review group (ERG) and NICE committee in both TA439 and TA709 and has been used in other oncology TAs where OS data is immature, as discussed in NICE Decision Support Unit (DSU) technical support document (TSD) 19.[171] The model choice in TA709 was considered by the ERG to be appropriate to capture all relevant health states and clinically plausible transitions between health states.[1] By contrast, TA716 applied a partitioned survival approach and the ERG considered the OS data used to inform the model to be immature with heavy censoring at the end of the KM curve possibly resulting in implausible plateaus in the survival curves.[172] For these reasons, the ERG stated that a state transition model where PPS is explicitly modelled, and OS depends on the time spent in the progression-free and progressed disease health states should have been considered.

The economic model utilises three health states (progression-free, progressed disease and death) to reflect disease course, and the subsequent cost and utility consequences of different health states. The model structure has been chosen to

reflect the most important treatment outcomes for most dMMR/MSI-H mCRC patients: survival (progression free and overall) and quality of life. The model also accounts for adverse events.

All analyses within this submission have been conducted from the payer perspective, in this case the NHS and personal social services (PSS). Key assumptions were validated by medical/clinical oncologists specialising in colorectal cancers.

B.3.2.1 Patient population

The economic evaluation considers the use of NIVO + IPI for the treatment of previously untreated patients aged 12 years and over with dMMR/MSI-H mCRC, in line with the anticipated licensed indication.

Three base case analyses are presented, reflecting the potential patient populations in the UK:

- **Adult population Table 50**: informed by baseline patient parameters are derived from the baseline characteristics of patients enrolled across the NIVO + IPI and chemotherapy arms of the CM8HW study.
- **Adolescent population (Table 51**): informed by UK statistics for CRC and the adolescent population.
- **Weighted population (Table 52**): a weighted analysis using published statistics describing UK mCRC diagnoses, incorporating the adult and adolescent population.

Table 50. Baseline patient parameters: adult population

Parameter	Mean	SE	Source
Baseline age (years)	60.9	0.82	Pooled ITT population within NIVO + IPI and chemotherapy arm of CM8HW[114]
Proportion of cohort female	53.8%	10.76%†	
Body weight (kg)	[redacted]	[redacted]	
Mean body surface area (m^2)	[redacted]	[redacted]	

†Assumed 20% of mean value

Abbreviations: IPI, ipilimumab; ITT, intention to treat; NIVO, nivolumab; SE, standard error

Table 51. Baseline patient parameters: adolescent population

Parameter	Mean	SE	Source
Baseline age (years)	14.5	1.70	Calculated from ONS population estimates for the UK, mid-2022, using data for age 12-17 years[173]
Proportion of cohort female	64.3%	12.86%†	Proportion of female cases reported in UK 2016–2018 for age 10–19 years[174]
Body weight (kg)	49.6	9.93†	Weighted average of weight for 14-year old boy and 14-year old girl, as reported in BNF[175]
Mean body surface area (m^2)	1.5	0.3†	Body surface area for child weighing 49-50kg, as reported in BNF[176]

†Assumed 20% of mean value

Abbreviations: BNF, British National Formulary; ONS, Office for National Statistics; SE, standard error

Table 52. Baseline patient parameters: weighted population

Parameter	Adult mean	Adolescent mean	Weighted mean	SE	Source
Baseline age (years)	60.9	14.5	60.85	12.17*	Weighted mean of adult and adolescent values, weighted using proportion of CRC diagnoses in age 10–19 years versus overall patient cohort (0.098%)[174]
Proportion of cohort female	53.80%	64.30%	53.81%	10.76%*	
Body weight (kg)	70.5	49.6	70.5	14.10*	
Mean body surface area (m^2)	1.78	1.5	1.78	0.356*	

†Assumed 20% of mean value

Abbreviations: CRC, colorectal cancer; SE, standard error

B.3.2.2 Model structure

The progression of disease in mCRC patients typically includes a period without disease advancement following initial treatment, during which it is possible for patients to remain in the progression-free health state. After this phase, patients may experience disease progression, die from mCRC without a formal diagnosis of progression, or die from unrelated causes. During the progression phase, patients

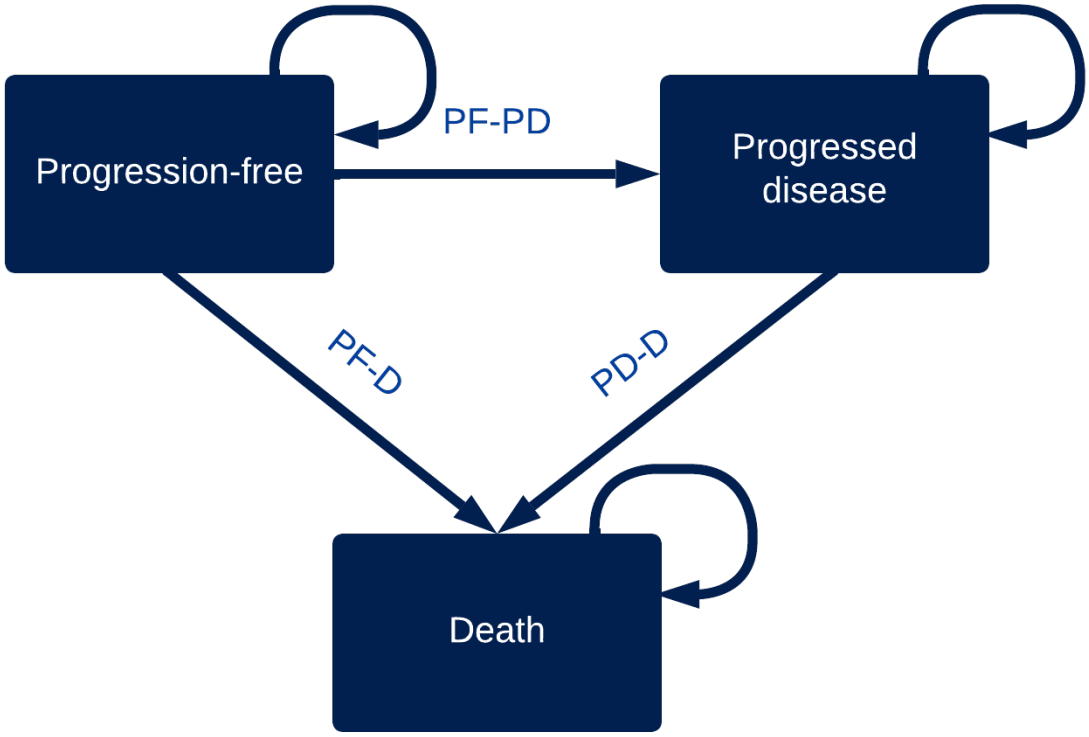
generally continue to receive treatment for progressed disease and ultimately will die from either mCRC or other causes.

The clinical course of the disease, the available clinical data, and prior submissions for untreated mCRC patients (TA709 and TA439) resulted in development of a 3-state semi-Markov model.[1,71] Figure 31 and Table 53 provide an overview of the generalised model framework including the transition pathways across the following health states:

- Progression-free disease (PF)
- Progressed disease (PD)
- Death (D)

The economic model also incorporates the cost and quality of life impact of adverse events (AEs) associated with initial treatments.

Figure 31. Three-state semi-Markov model structure



Abbreviations: D, death; PD, progressed disease; PF, progression-free

Table 53. Description of economic model transitions

Transition	Description	Submission section
Progression-free to progressed disease (PF-PD)	Time to progression (TTP), defined as time from model entry to progression	B.3.3.1
Progression-free to death (PF-D)	Pre-progression survival (PrePS), defined as time from model entry to deaths occurring before progression	B.3.3.2
Progressed disease to death (PD-D)	Post-progression survival (PPS), defined as time from progression to death	B.3.3.3

In this semi-Markov model, the cohort of patients moves through the three health states according to a set of transition probabilities, also called a transition probability matrix. The Markov framework models the structural relationships between health states. Advantages of this framework are that the projected survival estimates are "consistent" (PFS cannot be higher than OS) and it allows increased flexibility on assumptions regarding post-progression survival (PPS) e.g., if the progressed disease transition is time varying. Importantly, this method does not model survival endpoints independently, but rather focusses on estimating the structural relationship between PFS and OS in the trial data.

Thus, in this semi-Markov model, the transition probability from PD to D and the probability of remaining in progressed disease depend on the time spent in the progressed disease state. For PFS, time-varying estimates have been implemented in Markov models when all patients start in PFS, as the sojourn time will be equal to the model cycle length. However, due to the memoryless property of a conventional Markov model, varying these transitions according to time in the model for progressed disease is considerably more complex.

In the Microsoft Excel model, this is implemented in a Visual Basic for Applications (VBA) macro for efficiency purposes. Transition probabilities are estimated in a separate sheet for all transitions for all states for each treatment which are then loaded into the macro. In the macro, the health state occupancy is then calculated using a three-dimensional array where the rows are the state, the columns are the model cycle time, and the third axis is the time in the health state (sojourn time).

Using this three-dimensional array, the proportion of patients remaining within a health state is estimated for each model cycle *depending* on the time spent in the health state. For PFS, the time spent in the health state is equal to the model cycle length and, therefore, including the sojourn time does not make a difference. However, for progression, for each model cycle, the proportion of remainders for model cycle *t* is calculated by summing those patients with sojourn time (i.e., the time at which patients entered progression) smaller and equal to the model cycle time *t*.

A 28-day model cycle length is used in the model. Although several previous NICE health technology assessments (HTAs) for CRC used a weekly cycle length (including TA709[1] and TA716[172]), other models used a 28-day cycle length (TA242[177] and TA668[73]). Clinical events of interest occur less frequently than a monthly basis. During CM8HW, tumour assessment occurred every 6 weeks from randomisation to week 24 and every 8 weeks thereafter.[117] Further, TA709 assumed that patients visit a consultant once every two weeks with other disease monitoring applied once every 1–4 months. By comparison, comparator chemotherapy has a two- or three-week cycle length, so that a weekly cycle may not reflect clinical practice in terms of impact of discontinuation. As a result, a 28-day cycle length allows for treatment regimens to fit in a single model cycle while being sufficiently short to capture all relevant events of interest. The model cycle length is half-cycle corrected using the trapezoidal method.

Annual discount rates for costs and health effects are set to 3.5%, in line with NICE guidelines.[178]

B.3.2.2.1 Derivation of health state occupancy

Within the model, patients transition through the health states described above according to a set of transition probabilities informed by the following sources:

- PF to PD (Section B.3.3.1):
    - NIVO + IPI: time to progression data from CM8HW.
    - Chemotherapy: time to progression data from CM8HW.

    - PEMBRO: outcomes from PFS indirect comparison, detailed in Section B.2.7, applied to time to progression outcomes from CM8HW.

- PF-D (Section B.3.3.2): due to lack of data from CM8HW, general population mortality has been sourced from UK life tables, with all arms assumed to have equivalent outcomes, in line with UK clinical expert advice. CM142 pre-progression survival (PrePS, defined as time from model entry to deaths occurring before progression) data are used in scenario analysis.

- PD-D (Section B.3.3.3): due to lack of PPS data from CM8HW, data from CM142 is applied.

Table 54. Features of the economic analysis

	Previous evaluations	Current evaluation	
Factor	**TA709[1]**	**Chosen values**	**Justification**
Population	Adults (18+ years)	Adults and adolescents (12+ years)	Consistent with proposed marketing authorisation
Time horizon	40 years	40 years for adults and adolescents (extended time horizon for adolescents as sensitivity analysis)	Can be considered a lifetime horizon and therefore sufficiently long to capture all relevant costs and benefits
Model structure	A 3-state (PF, PD and death) semi-Markov model was the preferred model for assessing cost-effectiveness	3-state semi-Markov model (PFS, PD, death)	Consistent with the final TA709 analysis. In TA709, the ERG recommended using a semi-Markov model with three health states (PF, PD, death)
Treatment waning effect?	None	None	Post-progression survival is based on CM142 and incorporates the impact of treatment switching
Source of utilities	EQ-5D-3L utility values collected in KN-177 trial	EQ-5D-3L utility values collected in the CM-8HW trial	Consistent with TA709
Source of costs	NICE TA439[71], National schedule of NHS costs 2018-19[179], eMIT 2018[180], PSSRU[181] and published literature, BNF[182]	NICE TA709[125], National schedule of NHS costs 2021/2022[183], eMIT 2023[180], BNF[182], PSSRU 2022-2023[181] and published literature	Resource use is based on the most recent previous TAs in colorectal cancer (TA709 and published literature). Unit costs are taken from recognised national databases

Abbreviations: BNF, British national formulary; eMIT, electronic market information tool; EQ-5D3L, EuroQol 5-dimensional questionnaire (3 levels); NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, progression-free; PSSRU, Personal Social Services Research Unit; TA, technology assessment

B.3.2.2.2 Treatment sequences

Patients enter the economic model with previously untreated mCRC and can receive NIVO + IPI or a comparator treatment. Following treatment discontinuation, patients in all treatment arms can receive subsequent therapy, described in Section B.3.5.1.4.

Patients receiving immunotherapy (NIVO + IPI or PEMBRO) in the first-line setting are assumed to receive chemotherapy as a subsequent treatment. Patients receiving chemotherapy in the first-line setting are assumed to receive NIVO + IPI as a subsequent treatment, in line with TA716; alternatives are assessed through scenario analysis.[172]

B.3.2.2.3 Outcome measures

The primary model output is the incremental cost-effectiveness ratio (ICER) expressed as incremental costs per quality-adjusted life year (QALY) gained. 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.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Nivolumab plus ipilimumab

This cost-effectiveness analysis assesses NIVO + IPI for the treatment of previously untreated patients aged 12 years and over with dMMR/MSI-H mCRC, in line with the anticipated licensed indication. Evidence is derived from CM8HW, which reflects the UK patient population.

B.3.2.3.2 Comparators

PEMBRO can be considered a key comparator, as it is the only therapy specifically recommended for untreated dMMR/MSI-H mCRC.[1] Additionally, patients with untreated mCRC will typically receive FOLFOX, FOLFIRI or CAPOX, which the TA709 NICE appraisal committee has concluded are equally effective. A small number of patients (approximately 5-10% based on expert opinion) with RAS wild-type disease will receive panitumumab-based therapy or cetuximab-based therapy,

which TA709 has concluded are equally effective. A proportion of patients (around 5% based on expert opinion) with RAS-mutant disease would receive FOLFOXIRI, while a minority of patients would receive capecitabine monotherapy.

Hence, based on available NICE guidance in the mCRC population[1], the final scope and clinical opinion, the following comparators were deemed most appropriate[184]:

- PEMBRO
- FOLFOX
- FOLFIRI
- CAPOX
- Capecitabine
- FOLFOXIRI
- Panitumumab plus FOLFOX or FOLFIRI
- Cetuximab plus FOLFOX or FOLFIRI

In line with the approach taken in TA709, this cost-effectiveness analysis assumes that the chemotherapy arm of CM8HW reflects efficacy of all chemotherapy regimens (FOLFOX, FOLFIRI, cetuximab with FOLFOX or FOLFIRI, panitumumab with FOLFOX or FOLFIRI, CAPOX, capecitabine and FOLFOXIRI), with costs amended to reflect regimen. PEMBRO efficacy and costs are modelled as a separate comparator arm. Scenario analyses will assess the impact of individual chemotherapies.

B.3.3 Clinical parameters and variables

B.3.3.1 Progression-free to progressed disease (PF-PD)

The transition between the progression-free and progressed disease states is informed by an analysis of time to progression (TTP) data, wherein progression

events are defined as per the CM8HW primary PFS definition and data are censored at subsequent treatment or death events.

As outlined above, TTP data from CM8HW was leveraged for NIVO + IPI and chemotherapy. As no direct evidence is available comparing PEMBRO with NIVO + IPI in dMMR/MSI-H mCRC patients, several indirect treatment comparison (ITC) approaches have been used to provide comparative evidence for PEMBRO versus NIVO + IPI; these have been used to derive PEMBRO TTP data.

B.3.3.1.1 Nivolumab plus ipilimumab

The PF-PD transition was estimated by fitting parametric models to the TTP data from CM8HW. In the NIVO + IPI arm, the median TTP (Figure 32) was [redacted]), while among chemotherapy patients the median TTP was [redacted]. In the NIVO + IPI arm, the one-year progression-free probability was [redacted] while in the chemotherapy arm it was [redacted] The calculated HRs between the two trial arms, under the proportional hazards assumption (PHA), was [redacted]

Figure 32. CM8HW time-to-progression KM curves

Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIV, nivolumab

A full description of methods used to undertake parametric extrapolation is provided in Appendix O, while a brief overview is provided below.

B.3.3.1.1.1 Extrapolation approach

Proportional hazards assessment

In accordance with NICE DSU TSD 14,[185] the validity of the PHA was assessed for the PF-PD transition to inform the choice between dependent and independent parametric models. To determine whether the PH assumption held, the time dependency of the HRs was tested, which is equivalent to testing for a non-zero slope in a generalized linear regression of scaled Schoenfeld residuals over time, where a non-zero slope indicates a violation of the PH assumption. A visual inspection of the scaled Schoenfeld residuals plot against time, as well as the log-cumulative hazard plot against log-time, were considered in the determination of PH between treatments. The chi-square test was also used to test whether the slope was zero.

The scaled Schoenfeld residuals plot is shown below in Figure 33 for the PF-PD transition. The p-value obtained on the non-zero slope test was [redacted], indicating that hazards do not remain constant over time. The log-cumulative hazard plot against log-time is also shown below in Figure 34. For patients receiving NIVO + IPI versus chemotherapy, the log-cumulative hazards are not parallel and cross several times. Therefore, the PH assumption is rejected and, as a result, only independent curves were fitted.

Figure 33. CM8HW scaled Schoenfeld residuals plot for chemotherapy vs NIVO + IPI TTP

Abbreviations: IPI, ipilimumab; NIV, nivolumab; TTP, time to progression

Figure 34. CM8HW log-cumulative hazards plot for chemotherapy vs NIVO + IPI TTP

Abbreviations: IPI, ipilimumab; NIV, nivolumab; TTP, time to progression

Independent parametric fitting

Standard parametric models (exponential, gamma, generalised gamma, Gompertz, log-logistic, lognormal, Weibull) were fitted to CM8HW TTP data as per NICE DSU TSD 14 and 21 and used to extrapolate beyond the trial period.[171,185] Identification of the best model fit was based on the model selection algorithm outlined in Palmer et al., (2023),[186] as well as via statistical tests such as the Akaike information criterion (AIC). Besides using AIC scores to aid in model selection, standard parametric model fits were compared against survival curves generated from external data sources. Additionally, the results produced from extrapolation were validated by clinical experts during advisory board meetings to ensure that the extrapolations are clinically plausible.

The resulting AIC values for all parametric extrapolations can be found in Table 55 below. Extrapolated curves can be found in Figure 35 and Figure 36, and landmark survival values can be found in Table 56.

Of the parametric models, the exponential and Gompertz can be excluded immediately based on unrealistic extrapolations as seen in Figure 36, with the

exponential predicting a steep decline in TTP and the Gompertz predicting an unrealistically high long-term TTP. Of the five remaining candidate fits, the generalised gamma, lognormal, and log-logistic fits had the lowest AIC values.

Looking at the extrapolations in Figure 36, the generalised gamma fit provides a more optimistic extrapolation than both log-logistic and lognormal, which behave comparably to one another. This is further supported by the landmark survival estimates found in Table 56, with the generalised gamma fit having a median TTP of [redacted] years (95% CI: [redacted]) while log-logistic had a median TTP of [redacted] years (95% CI: [redacted]) and lognormal [redacted] years (95% CI: [redacted]). However, the generalised gamma provides the closest fit to the data in the first six months, as the only curve to capture the hazard profile shape of the observed data. Given the significantly lower AIC value for the generalised gamma model ([redacted] versus [redacted] for log normal and [redacted] for log logistic), the generalised gamma fit was chosen as the base case for the economic model.

Table 55. CM8HW NIVO + IPI TTP AIC values (lowest AIC in bold)

TTP	CM8HW NIVO + IPI AIC
Exponential	[redacted]
Gamma	[redacted]
Generalized gamma	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Lognormal	[redacted]
Weibull	[redacted]

Abbreviations: AIC, Akaike information criterion; TTP, time to progression

Figure 35. CM8HW NIVO + IPI TTP standard parametric fits to end of trial period

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; TTP, time to progression

Figure 36. CM8HW NIVO + IPI TTP standard parametric fits beyond trial period

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; TTP, time to progression

Table 56. CM8HW NIVO + IPI TTP parametric fit landmark survival estimates

	Median TTP, years (95% CI)	Landmark progression-free probability estimates (95% CI)			
		1 year	5 years	10 years	20 years
Observed					
Exponential					
Gamma					
Generalised gamma					
Gompertz					
Log logistic					
Log normal					
Weibull					

Abbreviations: CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; TTP, time to progression

B.3.3.1.1.2 Clinical validation of long-term outcomes

In order to ensure face validity of the parametric model, validation of the extrapolated model results was carried out against external sources.

The estimates of the median TTP, one-year, two-year, and five-year progression-free probability generated by the extrapolation of the CM8HW NIVO + IPI arm were compared against PFS data from CM142 Cohort 1 (2L+ mCRC receiving NIVO monotherapy), Cohort 2 (2L+ mCRC receiving NIVO + IPI) and Cohort 3 (1L mCRC receiving NIVO + IPI), as described in Table 57. TTP and PFS cannot be considered interchangeable, as TTP is defined as time from randomisation to progression with censoring for death events whereas PFS is defined as time from randomisation to progression or death. As such, PFS will be expected to be lower than TTP. However, as mortality is low prior to progression, PFS can be used to assess face validity of TTP estimates.

CM142 cohort 3 (1L NIVO + IPI) PFS was higher than TTP predicted by all CM8HW extrapolations at years 1 and 2, indicating that all extrapolations may be slightly conservative during this period. However, by year 5, CM142 Cohort 3 PFS was higher than lognormal and log-logistic TTP and lower than generalised gamma TTP, indicating that the generalised gamma extrapolation may have more face validity at this point.

In support of this, PFS in CM142 Cohort 2 (2L+ NIVO + IPI) was comparable with TTP for the lognormal and log-logistic extrapolations at five years, indicating that these extrapolations are highly conservative.

PFS for the CM142 Cohort 1 (2L+ NIVO monotherapy) was lower at all time points compared with TTP from CM8HW NIVO + IPI treatment arm extrapolations, as can be expected based on regimen and treatment history.

This comparison demonstrates that the generalised gamma extrapolation has the most face validity. Lognormal and log-logistic extrapolations can be considered highly conservative but may still be plausible. More conservative extrapolations, such as exponential, gamma, Weibull and Gompertz, appear to lack face validity at five years.

Table 57. Comparison of landmark survival values for CM8HW NIVO + IPI TTP extrapolation versus CM142 observed values

		Median, years (95% CI)	1-year progression-free	2-year progression-free	5-year progression-free
CM8HW NIVO + IPI	Observed TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic TTP	[redacted]	[redacted]	[redacted]	[redacted]
CM142[120,121]	Cohort 1 (2L+ NIVO) PFS	1.2	[redacted]	[redacted]	34%[84]
	Cohort 2 (2L+ NIVO + IPI) PFS	NR	71%	60%	52%[84]
	Cohort 3 (1L NIVO + IPI) PFS	NR	77%[120]	71%[120]	55%[121]

TTP defined as time from randomisation to progression, censored at subsequent treatment or death events. PFS defined as time from randomisation to progression or death, censored at subsequent treatment. PFS will be expected to be lower than TTP. However, as mortality is low prior to progression, PFS can be used to assess face validity of TTP estimates.

Abbreviations: CI, confidence interval; IPI, ipilimumab; NE, not evaluable; NIVO, nivolumab; NR, not reached; PFS, progression-free survival; TTP: time to progression.

B.3.3.1.2 Chemotherapy

As outlined in Section B.3.3.1.1, the transition from PF-PD was estimated by fitting parametric models to the TTP data from CM8HW. In accordance with NICE DSU TSD 14,[185] the validity of the PHA was assessed for the PF-PD transition to inform the choice between dependent and independent parametric models. However, the PHA is rejected, and as a result only independent curves were fitted.

B.3.3.1.2.1 Extrapolation approach

As previously, standard parametric models (exponential, gamma, generalised gamma, Gompertz, log-logistic, lognormal, Weibull) were fitted to CM8HW TTP data as per NICE DSU TSD 14 and 21 and used to extrapolate beyond the trial period.[171,185] Identification of the best model fit was based on the model selection algorithm outlined in Palmer et al., (2023),[186] as well as via statistical tests such as the AIC. Besides using AIC scores to aid in model selection, standard parametric

model fits were compared against survival curves generated from external data sources. Additionally, the results produced from extrapolation were validated by clinical experts during advisory board meetings to ensure that the extrapolations are clinically plausible.

The AIC values for all PF-PD fits to the CM8HW chemotherapy data can be found in Table 58 below. Extrapolated curves can be found in Figure 37 and Figure 38, and landmark survival values can be found in Table 59.

All parametric models show similar shapes within the observed time window of 1.25 years, shown in Figure 37. The AIC values of all models fall between 687.2 (log normal) and 697.9 (Weibull), so none can be immediately eliminated based solely on AIC. In the long-term extrapolations shown in Figure 38, the Gompertz fit has the most optimistic long-term TTP progression-free probability, while the exponential and Weibull fits have the least optimistic. Of the extrapolations falling between these extremes, the three with the lowest AIC values (Table 58) in order were lognormal (687.2), generalised gamma (687.4), and log-logistic (688.1). Comparing the landmark survival values, Table 59 shows that generalised gamma and log-logistic both precisely match the observed median TTP of [redacted] months, while the lognormal point estimate is slightly higher at [redacted] months. However, the 95% CI bounds for all fits are overlapping. At the 1-year mark, all three models are again comparable to the observed. At 5 years and beyond, the behaviour of the lognormal and log-logistic models is identical, with estimates for both slightly lower than the generalised gamma predictions. Given the comparable performance of the lognormal and generalised gamma fits, and that generalised gamma was recommended for NIVO + IPI, it is also recommended here for chemotherapy for consistency. Generalised gamma also provides a more optimistic long-term extrapolation for chemotherapy compared with lognormal and log-logistic.

Table 58. CM8HW chemotherapy TTP AIC values (lowest AIC in bold)

TTP	CM8HW chemotherapy AIC
Exponential	[redacted]
Gamma	[redacted]
Generalised gamma	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Lognormal	[redacted]
Weibull	[redacted]

Abbreviations: AIC, Akaike information criterion; TTP, time to progression

Figure 37. CM8HW chemotherapy TTP standard parametric fits to end of trial period

Abbreviations: TTP, time to progression

Figure 38. CM8HW chemotherapy TTP standard parametric fits beyond trial period

Abbreviations: TTP, time to progression

Table 59. CM8HW chemotherapy TTP parametric fit landmark survival estimates

	Median TTP, months (95% CI)	Landmark progression-free probability estimates (95% CI)			
		1 year	5 years	10 years	20 years
Observed					
Exponential					
Gamma					
Generalised gamma					
Gompertz					
Log-logistic					
Lognormal					
Weibull					

Abbreviations: CI, confidence interval; NR, not reached; TTP, time to progression

B.3.3.1.2.2 Clinical validation of long-term outcomes

As previously, the extrapolated TTP estimates for the CM8HW chemotherapy arm were validated against PFS outcomes from the published literature, i.e., Tougeron et al., (2020)[96] and chemotherapy PFS data from KN-177 published by Diaz et al., (2022).[69] As noted previously, TTP and PFS cannot be considered interchangeable, as TTP is defined as time from randomisation to progression with censoring for death events whereas PFS is defined as time from randomisation to progression or death. As such, PFS will be expected to be lower than TTP. However, as mortality is low prior to progression, PFS can be used to assess face validity of TTP estimates.

As outlined in Table 60, the median estimated TTP for the CM8HW chemotherapy arm is relatively similar to the estimated value in both validation sources and lie within the 95% CIs of both validation estimates. With regards to the estimated landmark survival values, the 95% CI of all 3-year CM8HW extrapolations encompass the estimated 3-year PFS from KN-177.[69] At 5-years, the generalised gamma extrapolated fit TTP for CM8HW validates the best to KN-177.[69]

Table 60. Comparison of landmark survival values for CM8HW chemotherapy TTP extrapolation versus Tougeron et al., (2020)[96] and KN-177[69]

		Median, years (95% CI)	1-year progression-free	3-year progression-free	5-year progression-free
CM8HW chemotherapy	Observed TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic TTP	[redacted]	[redacted]	[redacted]	[redacted]
Tougeron et al. (2020)	1L chemotherapy PFS	6.0 (5.0, 7.8)	-	-	-
KN-177	1L chemotherapy PFS	8.2 (6.2, 10.3)	-	13%	8%

TTP defined as time from randomisation to progression, censored at subsequent treatment or death events. PFS defined as time from randomisation to progression or death, censored at subsequent treatment. PFS will be expected to be lower than TTP. However, as mortality is low prior to progression, PFS can be used to assess face validity of TTP estimates.

Abbreviations: CI, confidence interval; NR, not reached; PFS, progression-free survival; TTP, time to progression.

B.3.3.1.3 Pembrolizumab

As no direct evidence is available comparing PEMBRO with NIVO + IPI in dMMR/MSI-H mCRC patients, several ITC approaches have been used to provide comparative evidence for PEMBRO PFS versus NIVO + IPI PFS. Based on the economic model structure, these ITCs would ideally compare the TTP between PEMBRO and NIVO + IPI. However, this data is unavailable for KN-177 as only PFS data is published (i.e., death events are included as events rather than censors, as per TTP definition). To enable a comparison of similar data across trials, the ITCs estimated the comparative efficacy for the outcome PFS of NIVO + IPI versus PEMBRO.

This economic model assumed that the HR between treatments for PFS would be approximately comparable with the HR of TTP. This assumption can be considered appropriate as KN-177 reported that the majority of PFS events were progression events rather than deaths (PEMBRO: 17 death events within PFS endpoint, 11.1% of ITT population; chemotherapy: 27 death events within PFS endpoint, 17.5%).[187]

The ITC feasibility assessment, outlined in Section B.2.7.1 found that CM8HW and KN-177 were sufficiently comparable in terms of inclusion and exclusion criteria, the common comparator (chemotherapy) treatments, outcome definitions and study design. Furthermore, the two trials were comparable across most of the baseline characteristics assessed, with only minor differences noticed in the distribution of race of patients. However, the PHA was violated, indicating that constant HR-based ITC methods may be biased. As a result, three approaches were recommended for the ITC:

- Fractional polynomial network meta-analysis (NMA), which does not require adjustment of data and does not require the PHA to hold.
- Anchored or non-anchored matching-adjusted indirect comparison (MAIC), which allows for adjustment of present heterogeneity in treatment effect modifiers without requiring PHA to hold.

- HR-based NMA to serve as a scenario analysis even though PHA is violated.

Given the minor differences in patient population and treatment effect modifiers, the fractional polynomial NMA is likely to be most appropriate. The base case analysis uses outcomes from the time varying hazard NMA to derive TTP transition rates for PEMBRO, as detailed below. Scenario analyses apply HRs from alternative ITC approaches.

PEMBRO TTP transition probabilities

To obtain PEMBRO TTP transition probabilities, the NIVO + IPI transition probabilities were converted to a rate and multiplied with the HRs obtained from the ITCs (fractional polynomial as a base case analysis) according to the following formula:

$$Transition\ rate\ PEMBRO = \frac{-\ln(1 - per\ cycle\ NIVO + IPI(\ p))}{cycle\ length} * HR$$

Hereafter, the transition rate was converted back to a 28-day transition probability:

$$Transition\ probability\ PEMBRO = 1 - e^{-transition\ rate\ PEMBRO\ *\ cycle\ length}$$

Clinical validation to observed KN-177 outcomes is provided in Section B.3.13.1.1.

B.3.3.2 Progression-free to death (PF-D)

For the PF-D transition, there are limited data sources that can be used to estimate the PF-D transition. As noted above, the majority of PFS events during the KN-177 study were progression events, with death events occurring in 11.1% of the PEMBRO arm and 17.5% in the chemotherapy arm after median follow-up of 28.4 months.[187] While this can be considered above general population mortality, there are few events from which to reliably extrapolate. Further, PrePS (informing the PF-D transition) appears to be slightly worse for patients receiving chemotherapy.[187]

Clinical experts from the UK advisory board stated that general population mortality is likely to be representative of the PF-D transition for dMMR/MSI-H mCRC patients. It is possible that this assumption may underestimate mortality, particularly for patients receiving chemotherapy. However, use of general population mortality includes the inherent assumption that treatment choice does not impact on PrePS. As patients receiving chemotherapy may have slightly worse PrePS, this assumption

can be considered conservative. As a result, the base case analysis applies general population mortality.

Annual probabilities of mortality for the general population were obtained from UK life tables.[188] These annual probabilities were converted to a rate and then into 28-day probabilities, in line with the model cycle length, using the following equation:

$$Pcycle = 1 - e^{\left(-\left(\frac{-\ln(1-Pannual)}{weeks\ per\ year}\right) x\ cycle\ length\right)}$$

CM142 PrePS data were available to inform the PF-D transition. However, there were few events that occurred during the trial, leading to uncertainty. As a result, use of the CM142 is considered as a scenario analysis.

B.3.3.3 Progressed disease to death (PD-D)

For the PD-D transition, CM142 data were used in lieu of CM8HW data as CM8HW OS data were unavailable.

It is assumed that PPS is equal between the NIVO + IPI, PEMBRO and chemotherapy treatment arms. CM142 data were used to estimate the PD-D transition. Use of CM142 data is justified as CM142 data were comparable with that of CM8HW, as outlined below in Section B.3.3.3.2. An assumption of equivalence is appropriate as this assumption aligns with TA709, as outlined in Section B.3.3.3.1.

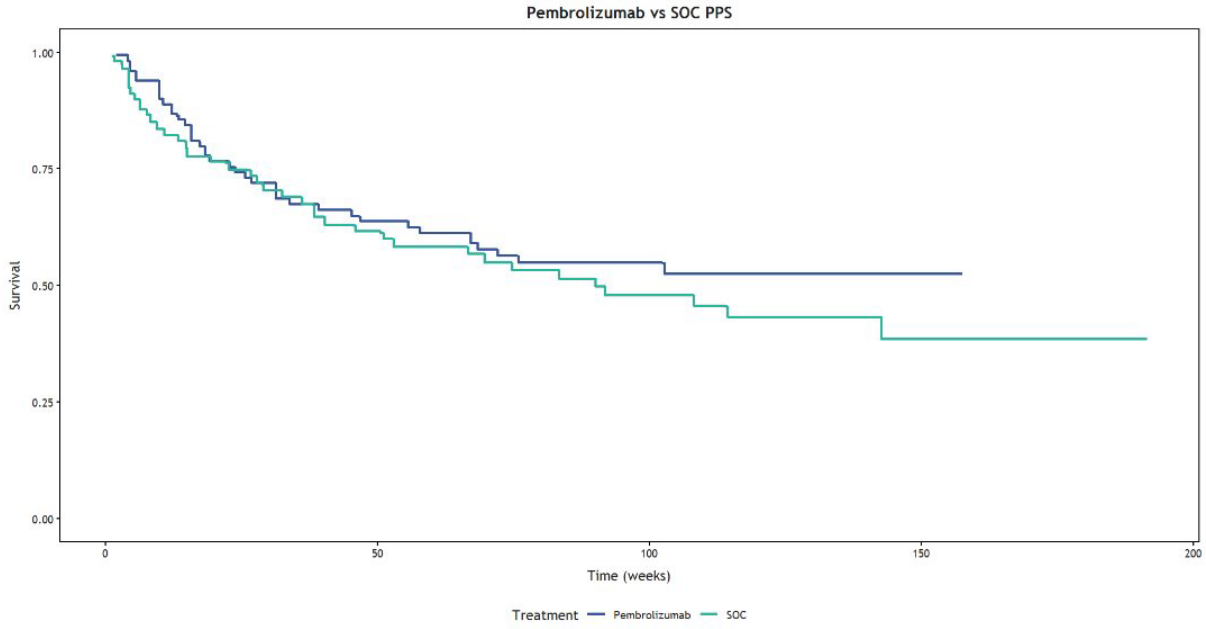
B.3.3.3.1 Assumption of equivalent post-progression survival

It is assumed that PPS (PD-D transition) was equivalent between treatment arms. This assumption aligns with that made in TA709,[1] where OS for the KN-177 trial was immature requiring an assumption to inform PPS. Subsequent treatment was assumed to be broadly equivalent between PEMBRO and chemotherapy so that PPS was assumed to be equivalent between PEMBRO and chemotherapy.[1] The assumption made in TA709 was accepted by the external assessment group (EAG), who found that the company's simplified assumption of equal PPS for all treatment arms in the model may be more acceptable than adjusting for OS through crossover adjustment due to the immaturity of their OS data.[1] As the target patient populations of KN-177 and CM8HW are similar and the interventions in both trials are somewhat

comparable in terms of mechanisms of action, the approach applied in TA709 with respect to accounting for immature OS data is also utilised in this analysis.

In support of this approach, an exploratory analysis of PPS of patients in KN-177 was conducted to determine if this assumption held. In this analysis, cumulative hazard curves from the PEMBRO submission to the CADTH were digitised and transformed to obtain the estimated PPS of the PEMBRO and chemotherapy arms.[189] It was found that the PPS between patients receiving PEMBRO and chemotherapy were comparable, implying that the assumption made above may hold where subsequent treatments are equivalent (Figure 39). Note that extrapolations could not be fit to the PPS for this analysis, as the numbers at risk for each treatment arm could not be derived from the published Canadian Agency for Drugs and Technologies in Health (CADTH) submission.[189]

Figure 39. KN-177 exploratory PPS KM curves



Abbreviations: KM, Kaplan-Meier; PPS, post-progression survival

B.3.3.3.2 Applicability of CM142

It is assumed that patients receiving NIVO + IPI in CM142 (Cohort 2 [2L+ NIVO + IPI] and 3 [1L NIVO + IPI]) are comparable to those in CM8HW, as they received similar treatment assignments as shown in Table 61 below.

Table 61. Dose assignments for the NIVO + IPI arms in CM8HW and CM142

Treatment	Drug	Dosing per administration		Dosing frequency
CM8HW NIVO + IPI dosing				
NIVO + IPI	NIVO	240	mg	Q3W for doses 1–4
	Ipilimumab	1	mg/kg	Q3W for doses 1–4
	NIVO	480	mg	Q4W for dose 5 and onwards
CM142 NIVO + IPI dosing				
2L+ NIVO + IPI (Cohort 2, n=119)	NIVO	3	mg/kg	Q3W for doses 1–4
	IPI	1	mg/kg	Q3W for doses 1–4
	NIVO	3	mg/kg	Q2W for dose 5 and onwards
1L NIVO + IPI (Cohort 3, n=45)	NIVO	3	mg/kg	Q2W
	IPI	1	mg/kg	Q6W

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; Q2W, every 2 weeks, Q3W, every 3 weeks, Q4W, every 4 weeks, Q6W, every 6 weeks

Crucially, the main difference between both populations is that patients who receive NIVO + IPI in CM142 are comprised of 1L and 2L+ patients (cohorts 3 and 2, respectively), whereas patients in CM8HW receive NIVO + IPI as a first-line regimen. However, this difference does not appear to have a large impact on the survival outcomes of the NIVO + IPI arms of both trials, as it was found that the PFS of CM142 and CM8HW, as well as the TTP transition, are similar (Figure 40, Figure 41). Thus, use of CM142 OS data in the estimation of PD-D can be considered appropriate.

Figure 40. CM8HW and CM142 PFS NIVO + IPI KM curves

Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab

Figure 41. CM8HW and CM142 TTP NIVO + IPI KM curves

Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; TTP, time to progression

B.3.3.3.3 Extrapolation approach

The PD-D transition was informed by patients from CM142 Cohort 2 (2L+ NIVO + IPI) and 3 (1L NIVO+ IPI) who had experienced a progression event. A total of 57 patients within this patient population had experienced a progression event and were included in this analysis (Figure 42). PPS was defined as time from progression to death. The median time to death after experiencing a progression event was [redacted] months (95% CI: [redacted]), and the 1-year death-free probability after experiencing progressed disease was [redacted] (95% CI: [redacted]).

Figure 42. CM142 NIVO + IPI PPS KM data

Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; PPS, post-progression survival

The standard parametric models previously described were fit to the CM142 data. The AIC values for all fits can be found in Table 62 below. Extrapolated curves can be found in Figure 43 and Figure 44, and landmark survival values can be found in Table 63.

Table 62. CM142 NIVO + IPI post-progression survival AIC values (lowest AIC in bold)

PPS	CM142 NIVO + IPI AIC
Exponential	[redacted]
Gamma	[redacted]
Generalised gamma	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Lognormal	[redacted]
Weibull	[redacted]

Abbreviations: AIC, Akaike information criterion; IPI, ipilimumab; NIVO, nivolumab; PPS, post-progression survival

Figure 43. CM142 NIVO + IPI post-progression survival standard parametric fits to end of trial period

Abbreviations: IPI, ipilimumab; NIVO, nivolumab

Figure 44. CM142 NIVO + IPI post-progression survival standard parametric fits beyond trial period

Abbreviation: IPI, ipilimumab; NIVO, nivolumab

Table 63. CM 142 NIVO + IPI post-progression survival parametric fit landmark estimates

	Median PPS, months (95% CI)	Landmark progression-free probability estimates (95% CI)			
		1 year	5 years	10 years	20 years
Observed					
Exponential					
Gamma					
Generalised gamma					
Gompertz					
Log-logistic					
Lognormal					

Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; PPS, post-progression survival

Of the seven parametric models fit, the Gompertz can be excluded immediately based on unrealistic extrapolations as seen in Figure 44, where it predicts an unrealistically high long-term PPS. The exponential also fits poorly from 0–2 years, estimating survival that is implausibly high. Looking at the AIC values of the remaining candidate fits in Table 62, the log-logistic ([redacted]), Weibull ([redacted]) and gamma ([redacted]) fits had the lowest values. Among these, the log-logistic had the most optimistic long-term extrapolations (Figure 44 and Table 63) but the lowest median PPS at [redacted] months (95% CI: [redacted]) which was closest to the observed of [redacted] months (95% CI [redacted]). The landmark behaviour of the gamma and Weibull models is comparable out to 20 years, and the curves closely match out to the extrapolated 40 years in Figure 44. At 1 year and 5 years, all three models behave comparably to the observed data. Due to its slightly lower AIC value, the log-logistic model was chosen as the base case for the economic model.

B.3.3.4 Time on treatment

The economic model incorporates a time on treatment curve to inform the proportion of patients discontinuing treatment due to progression, AEs and maximal treatment benefit. The timing of these discontinuations was assumed to impact on the incidence of AEs, treatment costs and resource use.

B.3.3.4.1 Nivolumab plus ipilimumab and chemotherapy

CM8HW data were used to estimate time to treatment discontinuation (TTD) defined as the last dose date minus the first dose date + 1 divided by 30.4375 (days per month =365.25/12). The last dose date referred to the last dose across all study therapies within the multi-agent regimens. Time to treatment discontinuation was summarised using Kaplan-Meier methodology, where the last dose date was the event date for those subjects who were off study therapy. Patients who were still on study therapy were censored on their last dose date.

A total of 288 patients were reflected in this analysis: 200 in the NIVO + IPI arm (two excluded as no treatment received) and 88 in the chemotherapy arm (13 excluded

as no treatment received). Figure 45 illustrates TTD across both arms across a median follow up of 31.5 months (range: 6.1–48.4 months). At time of database lock, 42 patients in the NIVO + IPI arm and 6 patients in the chemotherapy arm were still receiving treatment and so were censored on their last dose date.

The median TTD was [redacted] months (95% CI: [redacted]) in the NIVO + IPI arm and [redacted] months (95% CI: [redacted]) in the chemotherapy arm. The one-year probability of remaining on treatment was [redacted] (95% CI: [redacted]) for NIVO + IPI and [redacted] (95% CI: [redacted]) for chemotherapy.

Kaplan-Meier estimates of TTD were near complete at the end of CM8HW follow-up, in that the number of patients at risk of discontinuation was [redacted] in the NIVO + IPI arm and [redacted] in the chemotherapy arm ([redacted]). As such the Kaplan-Meier curves themselves were used in the model to estimate TTD, ensuring complete consistency with the clinical trial data.

Figure 45. CM8HW TTD KM data

Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; TTD, time to treatment discontinuation

B.3.3.4.2 Pembrolizumab

As TTD data are not available from KN-177, a simplifying assumption is required to model time on treatment.

Table 64 provides a comparison of duration of therapy and exposure for CM8HW and KN-177. As can be seen there are differences between NIVO + IPI and PEMBRO, but these can be considered minor. As such, the economic model assumes that PEMBRO TTD is equivalent to NIVO + IPI TTD. Scenario analyses have been undertaken to assess the impact of this assumption.

Table 64. Comparison of duration of therapy during CM8HW and KN-177

	CM8HW[114]		KN-177[187]	
	NIVO + IPI	**Chemotherapy**	**PEMBRO**	**Chemotherapy**
N	200	88	153	143
Duration of therapy, months				
Mean	[redacted]	[redacted]	13.3	8.3
Median	[redacted]	[redacted]	11.1	5.7
Range	[redacted]	[redacted]	0, 30.6	0.1, 39.6
Duration of exposure, %†				
≥3 months	[redacted]	[redacted]	112 (73.2%)	104 (72.7%)
≥6 months	[redacted]	[redacted]	96 (62.7%)	65 (45.5%)
≥12 months	[redacted]	[redacted]	73 (47.7%)	32 (22.4%)

†Reported as >3 months, >6 months and >12 months for CM8HW
Duration of therapy does not reflect censoring of patients with ongoing treatment at time of database lock
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab

B.3.3.5 Adverse events

Treatment-related AEs are an inevitable consequence of any intervention, and these events are applied in the economic model, affecting the costs and QALYs accrued by patients on each intervention.

AEs were included in the model according to the following inclusion criterion:

- AEs of special interest to immunotherapies:

    - Non-endocrine events: diarrhoea/colitis, hepatitis, rash and pneumonitis.
    - Endocrine events: adrenal insufficiency, hyperthyroidism and hypophysitis.
- AEs grade ≥3 with an incidence of ≥5%.

Identification of AEs of special interest is aligned with advice to BMS from a UK advisory board attended by clinical experts and health economists. Incidence of these AEs has been identified based on treatment-related grade ≥3 AEs. Other AEs grade ≥3 with an incidence of ≥5%have been included to pragmatically model AEs that are most likely to cause differences in incremental outcomes.

Table 65 summarises AEs applied in the economic model.

Table 65. Incidence of AEs

	NIVO + IPI	PEMBRO	Chemotherapy
Grade ≥3 AEs of special interest to immunotherapies			
Diarrhoea	[redacted]	2.0%	4.5%
Hepatitis	[redacted]	2.6%	0%
Rash	[redacted]	0.7%	1.1%
Pneumonia	[redacted]	3.3%	3.4%
Adrenal insufficiency	[redacted]	1.3%	0%
Hyperthyroidism	[redacted]	0%	0%
Hypophysitis	[redacted]	0%	0%
Grade ≥3 AEs in severity with an incidence of ≥5%			
Asthenia	[redacted]	1.3%	5.7%
Decreased neutrophil count	[redacted]	0%	6.8%
Hypertension	[redacted]	7.2%	6.8%
Neutropenia	[redacted]	0%	15.9%

Source: CM8HW (NIVO + IPI and chemotherapy) and KN-177[21,187]

Abbreviations: AE, adverse events; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab

B.3.4 Measurement and valuation of health effects

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

ChM8HW included assessment of health-related quality of life during the study, which can be used to derive utility values for modelling analysis. Assessments of EuroQol 5-dimenstional, 3 level questionnaire (EQ-5D-3L) status were carried out prior to day 1 of each treatment cycle for cycles 1 to 3 (cycles 1 and 2: six weeks; cycle 3 = four weeks), and then every other cycle (every eight weeks) thereafter. EQ-5D-3L data were then collected during safety follow-up visits 1 and 2 and survival follow-up visits every three months.

Table 66. CM8HW alignment between treatment schedule and EQ-5D-3L assessment

Cycle	Day	NIVO	IPI	EQ-5D-3L assessment
1	1	240mg	1mg/kg	Prior
	22	240mg	1mg/kg	-
2	1	240mg	1mg/kg	X
	22	240mg	1mg/kg	-
3	1	480mg	-	X
4	1	480mg	-	-
5	1	480mg	-	X
……		…..	…..	…..
Follow up 1		-	-	X
Follow up 2		-	-	X
Survival follow ups		-	-	X

Abbreviations: EQ-5D-L, EuroQol 5-dimensional questionnaire (3 levels); IPI, ipilimumab; NIVO, nivolumab

The analysis included 303 patients with 2,437 utility index (UI) observations, including 202 patients ([redacted] observations) receiving NIVO + IPI and 101 patients ([redacted] observations) receiving chemotherapy. A full description of the methodology and outcomes from this analysis are provided in Appendix P; a brief overview is provided below.

The NIVO + IPI arm had a higher completion rate at all timepoints through the study, as seen in Table 68 and Figure 46. The completion of questionnaires was lower in both arms following progression.

Table 67. CM8HW EQ-5D-3L observations

	NIVO + IPI (N=202)		Chemotherapy (N=101)		Overall (N=303)	
	N	Obs.	N	Obs.	N	Obs.
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression						
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
On/Off Treatment						
On-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression and On/Off Treatment						
PF On-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PF Off-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD On-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD Off-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PD, progressed disease; PF, progression-free

To estimate mean EQ-5D-3L values for each health state required, both descriptive and mixed model approaches were used, assessing progression model health states (PF and PD). As an exploratory analysis, models were considered assessing on/off treatment model health states and progression and treatment health states. However, these were not considered appropriate to model based on previous NICE HTAs in this setting and are not discussed further.[1,172]

Date of progression was assigned based on the BICR-assessed PFS, aligned with the clinical statistical analysis plan. All models were run by treatment as well as overall (treatment arms combined). Descriptive statistics of EQ-5D-3L utilities values were summarized for each health state, including number of participants, the number of EQ-5D-3L assessments, and EQ-5D-3L mean, median, standard deviation, SE, interquartile range, minimum and maximum values.

Table 68. CM8HW EQ-5D completion rate

Assessment Timepoint	NIVO + IPI			Chemotherapy		
	Number of Completions	Out of Expected Population	Out of Randomised Population	Number of Completions	Out of Expected Population	Out of Randomised Population
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 77	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 101	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 117	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 125	[redacted]	[redacted]	[redacted]			
Week 133	[redacted]	[redacted]	[redacted]			
Week 141	[redacted]	[redacted]	[redacted]			
Week 149	[redacted]	[redacted]	[redacted]			
Follow-Up 1	[redacted]	[redacted]	[redacted]			

Assessment Timepoint	NIVO + IPI			Chemotherapy		
	Number of Completions	Out of Expected Population	Out of Randomised Population	Number of Completions	Out of Expected Population	Out of Randomised Population
Follow-Up 2	[redacted]	[redacted]	[redacted]			
Survival Follow-Up 1	[redacted]	[redacted]	[redacted]			
Survival Follow-Up 2	[redacted]	[redacted]	[redacted]			

Abbreviations: EQ-5D, EuroQol 5-dimensional questionnaire; IPI, ipilimumab; NIVO, nivolumab

Figure 46. CM8HW EQ-5D-3L observations by progression status and treatment arm

Abbreviations: EQ-5D-3L, EuroQol 5-dimensional questionnaire (3 levels); PD, progressed disease; PF, progression-free

A mixed model approach was used for estimation of mean utility values in each health state of interest to account for repeated EQ-5D-3L measurements per participant within a health state. The dependent variable in the models was the EQ-5D-3L utility value, and the health state was included as a fixed effect. For models by treatment, treatment was included as a fixed effect and an interaction between treatment and the other health states in the model was also a fixed effect. A random intercept was used to account for repeated measurements within each participant. An unstructured covariance structure was used.

AICs and BICs based on maximum likelihood approach were used to examine the extent of improvement in model fit after including treatment, where lower AIC and BIC values indicated better fit. The -2×log-Likelihood statistics were also presented, from which chi-square statistics were derived to evaluate statistical significance of added variables between nested models. The least square-means, standard errors, and 95% CIs for the value of EQ-5D-3L utility index from the mixed modelling approach from each health state were presented.

Outcomes from CM8HW are presented in Table 69. As can be observed, across the population, patients had improved utility scores in the progression-free state ([redacted]) versus the progressed disease state ([redacted]). PD and PF estimates for NIVO + IPI were higher than for chemotherapy, with the differences being statistically significant. However, in the NIVO + IPI, progressed disease utility scores are higher than progression-free, potentially due to a lower questionnaire completion rate.

Table 69. Progression health states EQ-5D-3L utility index: number of patients, observations and least squares mean estimates

	Health State	Model without Treatment	Model with Treatment		
		Overall	Overall	NIVO + IPI	Chemotherapy
Model 1 Progression (Progression-Free, Progressed Disease)					
Pt, n/obs, n	Overall	[redacted]	[redacted]	[redacted]	[redacted]
	Progression-free	[redacted]	[redacted]	[redacted]	[redacted]
	Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]
LS means (95% CI)	Overall	[redacted]	[redacted]	[redacted]	[redacted]
	Progression-free	[redacted]	[redacted]	[redacted]	[redacted]
	Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]
Difference in LS means (95% CI) [nivolumab plus ipilimumab–chemo]	Overall	Not applicable			[redacted]
	Progression-free	Not applicable			[redacted]
	Progressed disease	Not applicable			[redacted]

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol 5-dimensional questionnaire (3 levels); IPI, ipilimumab; LS, least squares; NIVO, nivolumab

B.3.4.2 Mapping

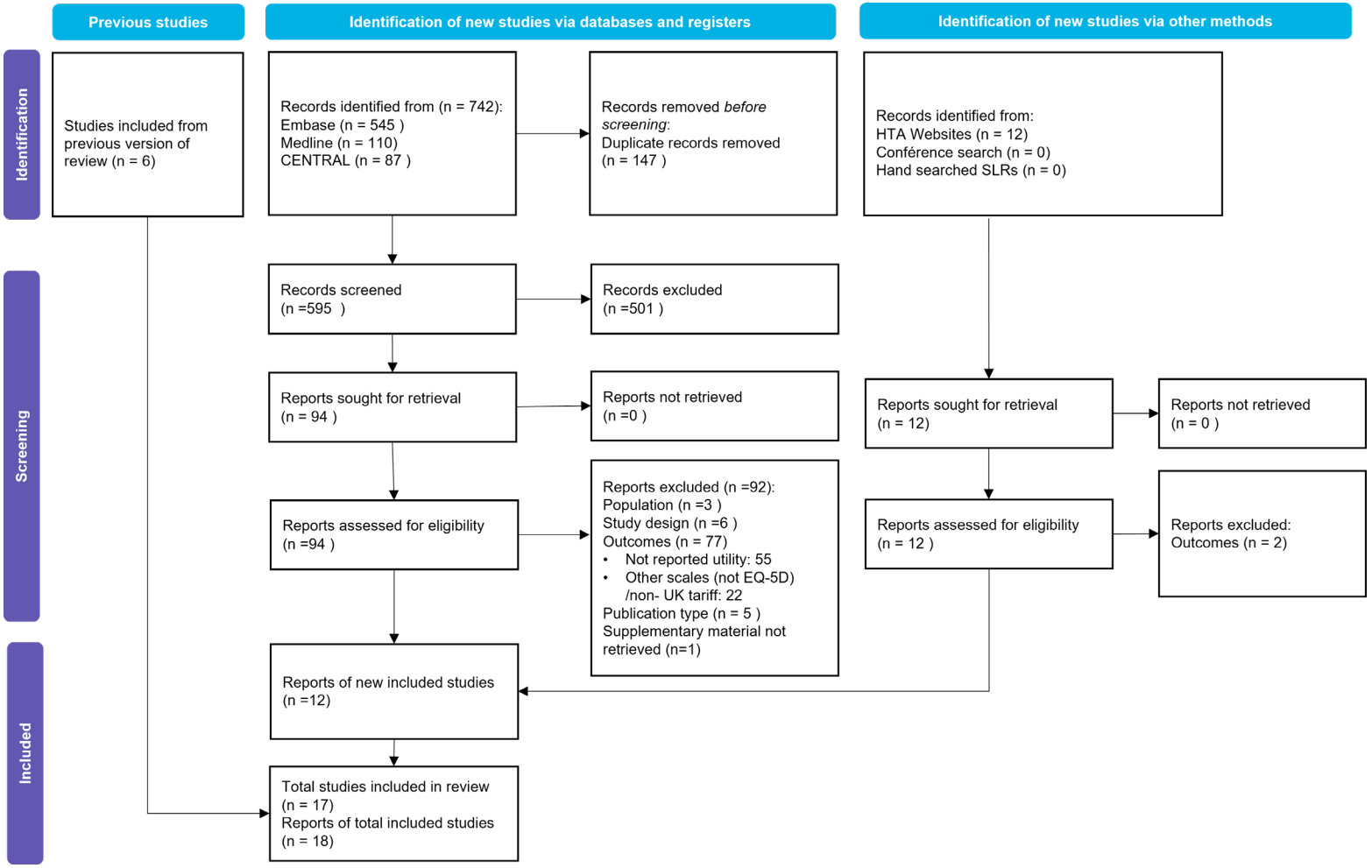
EQ-5D-3L was collected during CM8HW; therefore, no mapping algorithms were used between patient-reported outcomes and EQ-5D to derive utilities.

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

In line with NICE requirements, an SLR was conducted to identify health-related quality-of-life studies for the treatment of mCRC. A full description of SLR methodology and outcomes is provided in Appendix G. A brief overview is provided below.

In brief, electronic database searches (MEDLINE, Embase and Cochrane) searched from inception to 29 July 2021, and subsequently updated on 17 May 2024. Publications describing health state utility values and disutility values for metastatic colorectal cancer were included. The PRISMA diagram is provided in Figure 47. Eligible studies are described in Appendix H and were used to inform selection and validation of health-related quality of life data applied in the economic model.

Figure 47. PRISMA diagram illustrating the study selection process for identifying health-related quality of life studies



B.3.4.4 Adverse reactions

One-off disutilities due to AEs were estimated by multiplying the incidence of AEs for a specific treatment, the duration of the AEs and the disutilities of AEs. Total disutilities were then multiplied with the patients in the progression-free state in the first model cycle.

Evidence on disutilities of AEs in mCRC patients is lacking. Therefore, for many disutilities, estimates were derived from studies in other types of cancer. However, the majority of the utility values have been considered appropriate in previous NICE TAs (Table 70).

In a previous submission, the EAG recommended to limit the duration of the AE to 7 days based on expert opinion.[172] It was considered reasonable by clinical experts that the severity of AEs would be reduced sufficiently after 1 week resulting in grade 1–2 AEs, for which disutilities were not included in the model. The only exception were the endocrine AEs (adrenal insufficiency, hyperthyroidism, hypophysitis) where duration was considerably longer. These events were sourced from prior TAs.

Table 70. Disutilities per AE

Adverse event	Disutility		Duration (in model cycles)	
	Mean value	Reference	Mean value	Reference
Hepatitis	-0.2	Assumed equal to hypothyroidism/ asthenia based on Mai et al.[190]	0.25	TA439[71]
Neutropenia	-0.0607	TA439[71]	0.25	TA439[71]
Rash	-0.04	TA439[71]	0.25	TA439[71]
Diarrhoea/ colitis	-0.09	TA439[71]	0.25	TA439[71]
Adrenal insufficiency	-0.2	Assumed equal to hypophysitis based on Mai et al.[190]	3.8575	TA780,[191]
Hyperthyroidism	-0.069	Assumed equal to hypertension; TA439[71]	3.8575	TA780,[191]
Hypophysitis	-0.2	Assumed equal to hypothyroidism/ asthenia based on Mai et al.[190]	3.8575	TA780,[191]

Asthenia	-0.08	TA439[71]	0.25	TA439[71]
Decreased neutrophil count	-0.0375	TA439[71]	0.25	TA439[71]
Hypertension	-0.069	TA439[71]	0.25	TA439[71]
Increased lipase	-0.08	TA439[71]	0.25	TA439[71]
Pneumonia	-0.195	TA891[192],TA439[71]	0.25	TA439[71]

Abbreviations: AE, adverse event

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

The utility values used in the base case analysis are shown in Table 72 and were informed by analysis from CM8HW, which was conducted in a population relevant to the UK setting and provided data relevant to the reference case.

The utilities for the progression-free health state have been informed by the treatment-specific progression free utility data. This is appropriate given the statistically significant difference between the NIVO + IPI and chemotherapy arms during the utility analysis. Additionally, this has biological plausibility, given that NIVO + IPI is administered less frequently (every three weeks initially followed by every four weeks in the NIVO monotherapy phase) than chemotherapy comparators (biweekly) and infusions are shorter. Further, the safety profile of NIVO + IPI is favourable compared with chemotherapy despite a longer median treatment duration. Aligned with this, during TA709, the committee concluded that the use of treatment-specific utilities in the pre-progression setting is appropriate for decision making. This also aligns with recommendations from clinical experts in the UK advisory board.

There was also a statistically significant difference between NIVO + IPI and chemo in the progressed disease health state. However, use of these utilities in the economic model may lack face validity, potentially due to poor completion rates and censoring following subsequent treatment, particularly in the chemotherapy arm. As a result, a pooled progressed disease value has been used across all treatments. In the chemotherapy, this pooled progressed disease value is higher than the progression-free health state utility. Although the analysis censored patients on subsequent

treatment, a higher utility value in the progressed disease state may reflect clinical practice, as it may reflect high use of immunotherapies in the second-line setting, particularly NIVO + IPI.

For PEMBRO, treatment-specific health state utility data were not available. Therefore, it was assumed that PEMBRO utility values would be equal to NIVO + IPI. This assumption is based on research showing that health-related quality of life (HRQoL) is comparable between patients receiving NIVO + IPI and NIVO monotherapy.[193]

A comparison of CM8HW utility values versus previous mCRC HTAs is provided in Table 71. As can be seen, CM8HW values are lower than KN-177 values for both the immunotherapy and chemotherapy arms in the progression-free disease state. However, the progressed disease utility values are similar.

Table 71. Comparison of CM8HW utilities with previous CRC HTAs

		Progression-free	Progressed
CM8HW	NIVO + IPI	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
TA709 (N-177)	PEMBRO	0.843	0.730
	Chemotherapy	0.787	0.730
TA439	Cetuximab, panitumumab and chemotherapy	0.767	0.64

Abbreviations: CRC, colorectal cancer; HTA, health technology assessment; IPI, ipilimumab;

Table 72. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% confidence interval	Reference in submission (section and page number)	Justification
Health state utilities				
Progression-free (NIVO + IPI)	[redacted]	[redacted]	Section B.3.4.1 page 194	Derived from CM8HW and reflects statistically significant difference between treatment arms
Progression-free (chemotherapy)	[redacted]	[redacted]		
Progression-free (PEMBRO)	[redacted]	[redacted]		Assumed as NIVO + IPI
Progressed disease (all arms)	[redacted]	[redacted]		Derived from CM8HW
Adverse reactions				
Hepatitis	-0.2 (-0.04)	-	Section B.3.4.4 page 203	Assumption
Neutropenia	-0.0607 (-0.0457)	-		Derived from previous NICE appraisal
Rash	-0.04 (-0.008)	-		
Diarrhoea/colitis	-0.09 (-0.0379)	-		
Adrenal insufficiency	-0.2 (-0.04)	-		Assumption
Hyperthyroidism	-0.069 (-0.0138)	-		Assumption
Hypophysitis	-0.2 (-0.04)	-		Assumption
Asthenia	-0.08 (-0.0615)	-		Derived from previous NICE appraisal
Decreased neutrophil count	-0.0375 (-0.1438)	-		
Hypertension	-0.069 (-0.0138)	-		
Increased lipase	-0.08 (-0.016)	-		
Pneumonia	-0.195 (-0.039)	-		

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; SE, standard error

B.3.4.5.1 Age-adjusted utilities

The increasing prevalence of comorbidities in older aged cohorts and the adverse effect on HRQoL directly associated with age must be reflected in economic models with lifetime horizons. It can be assumed that the health state utility values for individuals without a particular health condition will change over the time horizon.

Hence, the economic model includes use of age-adjusted utility values over the time horizon of the model to account for this. This has been included in the economic model using the most recent 2022 UK recommendations for including age- and sex-adjusted utilities using the UK index of health state utility decline from Ara et al.[194-196]

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

Appendix I describes how relevant cost and healthcare resource data were identified.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Administration costs

The cost of administration for NIVO + IPI and comparators are detailed in Table 73. All immunotherapies were administered via intravenous (IV) infusion whereas chemotherapies were administered through complex IV infusion, with the exception of capecitabine monotherapy. Unit costs for drug administration were based on National schedule of NHS costs 2021–2022.[183] This is aligned with the approach used in TA709.[1]

Table 73. Administration costs for nivolumab plus ipilimumab and comparators

Component	NHS cost collection data	Cost	Intervention
Deliver Simple Parenteral Chemotherapy at First Attendance	National schedule of NHS costs 2021–2022 (SB12Z)[183]	£286.71	NIVO + IPI PEMBRO
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	National schedule of NHS costs 2021–2022 (SB14Z)[183]	£474.94	Chemotherapy
Deliver Exclusively Oral Chemotherapy	National schedule of NHS costs 2021–2022 (SB11Z)[183]	£216.90	Capecitabine monotherapy

Abbreviations: IPI, ipilimumab; NHS, National Health Service; NIVO, nivolumab; PEMBRO, pembrolizumab

B.3.5.1.2 Nivolumab plus ipilimumab

Drug acquisition costs were obtained from the BNF online database tool.[182] Table 74 provides the dose per vial and the costs per vial while Table 75 reports the dosing schedule per treatment; administration costs can be found in Table 73.

The cost per administration was estimated by identifying the lowest acquisition cost that could achieve the required dose. For the base case analysis, no vial sharing was assumed in line with best practice.

Table 74. Drug acquisition costs NIVO + IPI

Drug	Dose per vial	Cost per package	Reference
NIVO	40.0 mg	£439.00	BNF[182]
	100.0 mg	£1,097.00	
	240.0 mg	£2,633.00	
IPI	50.0 mg	£3,750.00	BNF[182]
	200.0 mg	£15,000.00	

Abbreviations: BNF, British National Formulary; IPI, ipilimumab; NIVO, nivolumab

Table 75. Dosing schedule and cost per cycle NIVO + IPI – adult population

Drug	Administration frequency	Dose per cycle	Treatment costs per cycle	References
NIVO	240mg Q3W for four treatment cycles	240mg	£2,633	CM8HW[114]
IPI	1mg/kg Q3W for four treatment cycles	70.5mg	£7,500	
NIVO	480 mg Q4W after 4 treatment cycles	480mg	£5,266	

Reflects dosing in adult patients. Adolescent population calculated using baseline characteristics in Table 51
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; Q3W, every 3 weeks, Q4W, every 4 weeks

B.3.5.1.2.1 Patient access scheme

A PAS has been applied, comprising a discount of [redacted] from the nivolumab list price and [redacted] from the ipilimumab list price. In order to best replicate the true economic impact of a positive recommendation for nivolumab and ipilimumab, the economic evaluation presented in this submission applies the PAS in the base case analysis.

Table 76. Acquisition cost of nivolumab following application of PAS

	24 ml vial	Cost per cycle	
		Cycle 1-4	Cycle 5+
No PAS	£2,633	£2,633	£5,266
PAS	[redacted]	[redacted]	[redacted]

Reflects dosing in adult patients. Adolescent population calculated using baseline characteristics in Table 51
Abbreviation: PAS, patient access scheme

Table 77. Acquisition cost of ipilimumab following application of PAS

	50 mg/10 ml vial	Cost per cycle
No PAS	£3,750	£7,500
PAS	[redacted]	[redacted]

Reflects dosing in adult patients. Adolescent population calculated using baseline characteristics in Table 51
Abbreviation: PAS, patient access scheme

B.3.5.1.3 Comparators

B.3.5.1.3.1 Pembrolizumab

Drug acquisition costs for immunotherapies were obtained from the BNF online database tool.[182] In Table 78, the dose per vial, the units per package and the costs per package and per mg can be found. Table 79 reports the dosing schedule per treatment and administration costs.

The cost per administration was estimated by identifying the lowest acquisition cost that could achieve the required dose. For the base case analysis, no vial sharing was assumed in line with best practice.

The base case analysis assumes use of the Q6W regimen as a conservative assumption.

Table 78. Drug acquisition costs PEMBRO

Drug	Dose per vial	Cost per package
PEMBRO	100.0 mg	£2,630.00

Table 79. Dosing schedule and cost per cycle for PEMBRO

Drug	Administration frequency	Dose per cycle	Treatment costs per cycle	References
PEMBRO	200mg Q3W	200.00 mg	£5,260.00	SmPC[182]
	400mg Q6W	400.00 mg	£10,520.00	

Reflects dosing in adult patients. Adolescent population calculated using baseline characteristics in Table 51

Abbreviation: PEMBRO, pembrolizumab

Patient access scheme

NHS England benefits from a PAS, comprising a simple discount from the PEMBRO price. BMS are not aware of the PAS discount available for PEMBRO and so is unable to include it in the base case analysis. Functionality is included in the economic model for the EAG to input a PAS discount for PEMBRO. However, it should be noted that this is not reflected in the results presented within this submission.

B.3.5.1.3.2 Chemotherapy

Costs of chemotherapy were based on the weighted average costs of several chemotherapy regimens: FOLFOX, FOLFIRI, CAPOX, Capecitabine, FOLFOXIRI, FOLFOX + cetuximab, FOLFIRI + cetuximab, FOLFOX + panitumumab, FOLFIRI + panitumumab.

Unit costs for these drugs were obtained from the eMIT 2023 and the BNF (Table 80).[180,182] The dosing schedule, administration frequency, and dose intensity were based on the CM8HW trial protocol for FOLFOX, FOLFIRI, cetuximab with FOLFOX and cetuximab with FOLFIRI; additional regimens were sourced from previous HTAs and SmPCs (Table 81). Chemotherapy was administered through complex IV infusion. The unit costs per chemotherapy regimen were weighted according to the proportion of patients receiving each regimen to estimate the total chemotherapy costs per model cycle (Table 82).

No vial sharing was assumed for any chemotherapy regimens.

Table 80: Drug acquisition costs for chemotherapies

Drug	Dose per tablet or vial	Units per package	Cost per package	Reference
Fluorouracil				
500 mg	500 mg	1	£3.43	eMIT 2023[180]
1000 mg	1000 mg	1	£3.04	eMIT 2023[180]
2500 mg	2500 mg	1	£4.12	eMIT 2023[180]
Leucovorin				
100 mg	100 mg	1	£4.56	eMIT 2023[180]
300 mg	300 mg	1	£19.28	eMIT 2023[180]
400 mg	400 mg	1	£126.25	BNF 2024[182]
Oxaliplatin				
50 mg	50 mg	1	£6.47	eMIT 2023[180]
200 mg	200 mg	1	£14.30	eMIT 2023[180]
Irinotecan				
500 mg	500 mg	1	£43.38	eMIT 2023[180]
Capecitabine				
150mg	150mg	60	£8.10	eMIT 2023[180]
300mg	300mg	60	£8.14	eMIT 2023[180]
500mg	500mg	120	£22.51	eMIT 2023[180]
Cetuximab				
100 mg	100 mg	1	£178.10	BNF 2024[182]
Panitumumab				
100 mg	100 mg	1	£379.29	BNF 2024[182]
400mg	400 mg	1	£1,517.16	BNF 2024[182]

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool

Table 81. Dosing schedule and cost per cycle of chemotherapies

Regimen	Dose	Unit	Dose frequency	Dose per cycle	Treatment cost per treatment cycle (£)	Total cost per treatment cycle (£)
FOLFOX						
Fluorouracil bolus – FOLFOX	400	mg/m^2	Q2W	712	8.24	59.02
Fluorouracil infusion – FOLFOX	2,400	mg/m^2	Q2W	4272		
Leucovorin – FOLFOX	400	mg/m^2	Q2W	712	36.48	
Oxaliplatin – FOLFOX	85	mg/m^2	Q2W	151.3	14.3	
FOLFIRI						
Irinotecan – FOLFIRI	180	mg/m^2	Q2W	320.4	43.38	88.10
Fluorouracil bolus – FOLFIRI	400	mg/m^2	Q2W	712	8.24	
Fluorouracil infusion – FOLFIRI	2,400	mg/m^2	Q2W	4272		
Leucovorin – FOLFIRI	400	mg/m^2	Q2W	712	36.48	
CAPOX						
Capecitabine–- CAPOX	1000	mg/m^2	Twice daily for 14 days followed by 7-day rest period	49000	16.28	35.35
Oxaliplatin – CAPOX	130	mg/m^2	Q3W	231.4	19.07	
Capecitabine						
Capecitabine–- Capecitabine	1250	mg/m^2	twice daily for 14 days followed by 7-day rest period	60200	21.71	21.71
FOLFOXIRI						
Fluorouracil infusion – FOLFOXIRI	3,200	mg/m^2	Q2W	5696	12.36	101.96
Leucovorin – FOLFOXIRI	350	mg/m^2	Q2W	623	31.92	
Oxaliplatin – FOLFOXIRI	85	mg/m^2	Q2W	151.3	14.30	

Regimen	Dose	Unit	Dose frequency	Dose per cycle	Treatment cost per treatment cycle (£)	Total cost per treatment cycle (£)
Irinotecan – FOLFOXIRI	165	mg/m^2	Q2W	293.7	43.38	
FOLFOX + cetuximab						
Fluorouracil bolus – FOLFOX + cetuximab	400	mg/m^2	Q2W	712	8.24	1,663.75
Fluorouracil infusion – FOLFOX + cetuximab	2,400	mg/m^2	Q2W	4272		
Leucovorin – FOLFOX + cetuximab	400	mg/m^2	Q2W	712	36.48	
Oxaliplatin – FOLFOX + cetuximab	85	mg/m^2	Q2W	151.3	14.30	
Cetuximab – FOLFOX + cetuximab	500	mg/m^2	Q2W	890	1,604.73	
FOLFIRI + cetuximab						
Irinotecan – FOLFIRI + cetuximab	180	mg/m^2	Q2W	320.4	43.38	£1,692.83
Fluorouracil bolus – FOLFIRI + cetuximab	400	mg/m^2	Q2W	712	8.24	
Fluorouracil infusion – FOLFIRI + cetuximab	2,400	mg/m^2	Q2W	4272		
Leucovorin – FOLFIRI + cetuximab	400	mg/m^2	Q2W	712	36.48	
Cetuximab – FOLFIRI + cetuximab	500	mg/m^2	Q2W	890	1,604.73	
FOLFOX + panitumumab						
Fluorouracil bolus – FOLFOX + panitumumab	400	mg/m^2	Q2W	712	8.24	1,955.47
Fluorouracil infusion – FOLFOX + panitumumab	2,400	mg/m^2	Q2W	4272		
Leucovorin – FOLFOX + panitumumab	400	mg/m^2	Q2W	712	36.48	
Oxaliplatin – FOLFOX + panitumumab	85	mg/m^2	Q2W	151.3	14.30	
Panitumumab – FOLFOX + panitumumab	6	mg/kg	Q2W	423	1896.45	

Regimen	Dose	Unit	Dose frequency	Dose per cycle	Treatment cost per treatment cycle (£)	Total cost per treatment cycle (£)
FOLFIRI + panitumumab						
Irinotecan – FOLFORI + panitumumab	180	mg/m^2	Q2W	320.4	43.38	1,984.55
Fluorouracil bolus – FOLFORI + panitumumab	400	mg/m^2	Q2W	712	8.24	
Fluorouracil infusion – FOLFIRI	2,400	mg/m^2	Q2W	4272		
Leucovorin – FOLFORI + panitumumab	400	mg/m^2	Q2W	712	36.48	
Panitumumab – FOLFORI + panitumumab	6	mg/kg	Q2W	423	1896.45	

Reflects dosing in adult patients. Adolescent population calculated using baseline characteristics in Table 51
Abbreviations: Q2W, every 2 weeks

Table 82. Total weighted chemotherapy costs per model cycle

Regimen	Advisory board opinion	Proportion weighting
FOLFOX	87.5%	29.17%
FOLFIRI		29.17%
CAPOX		29.17%
Capecitabine	0	0 (assessed in scenario)
FOLFOXIRI	5%	5%
FOLFOX + cetuximab	7.5%	1.875%
FOLFIRI + cetuximab		1.875%
FOLFOX + panitumumab		1.875%
FOLFIRI + panitumumab		1.875%

B.3.5.1.4 Subsequent treatment

The economic model incorporates subsequent treatments, which are documented in Table 83. During TA709, the economic model assumed that a large proportion of patients receive no second line treatment (approximately 46%), with remaining patients receiving FOLFOX, FOLFIRI or bevacizumab combination therapy.[1] However, in current UK clinical practice, patients who have progressed on previous treatment typically receive second-line immunotherapy (usually NIVO + IPI) or chemotherapy (usually FOLFOX or FOLFIRI).[172]

Patients receiving first-line immunotherapy will not receive second-line immunotherapy. As a result, patients in the NIVO + IPI and PEMBRO arms are assumed to receive second-line chemotherapy, which is assumed to be FOLFOX, as this has a lower cost than FOLFIRI. In the chemotherapy arm, eligible patients will receive second-line immunotherapy, which is usually NIVO + IPI;[172] PEMBRO is recommended by NICE only if patients cannot have NIVO + IPI.[65] Based on this rationale, patients in the chemotherapy arm are assumed to receive NIVO + IPI in the second-line setting. Scenario analyses have been conducted to assess the impact of alternative assumptions.

Table 83. Subsequent therapy applied in economic model

	Base case subsequent therapy	Justification
NIVO + IPI	Chemotherapy (FOLFOX)	Aligned with TA716 and lowest cost chemotherapy
PEMBRO	Chemotherapy (FOLFOX)	Aligned with TA716 and lowest cost chemotherapy
Chemotherapy	NIVO + IPI	Aligned with TA716

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab

These costs were estimated by dividing the total costs of subsequent treatment by the total duration of the treatment in days. This daily cost of treatment was then divided by the mean time in the progressed disease state for that specific intervention divided by the model cycle length. Costs per model cycle were then multiplied with the proportion receiving the subsequent treatment in question.

The mean time in progressed disease (1271.07 days) was estimated based on the restricted mean survival time (*t*=40) in the progressed disease state for the NIVO + IPI data from CM142, with PEMBRO and chemotherapy arms assumed to be equivalent. Costs per administration and the duration per course of subsequent treatment can be found in Table 84. The average administration costs were based on the costs per administration divided by the mean doses received.

Table 84. Subsequent treatment costs

Subsequent treatment	Cost per treatment cycle	Administration frequency	Weeks on subsequent treatment
FOLFOX	£54.90	Q2W	20.16
NIVO + IPI*	£10,133 £2,633	Q3W for first 4 cycles (excluding PAS) Q2W for subsequent cycles (excluding PAS)	104.36

Reflects dosing in adult patients. Adolescent population calculated using baseline characteristics in Table 51

*PAS discounts applied in base case analysis and relevant scenarios.

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PAS, patient access agreement; Q2W, every 2 weeks; Q3W, every 3 weeks

B.3.5.2 Health-state unit costs and resource use

B.3.5.2.1 Disease management and monitoring costs

Resource use estimates for the progression-free and progressed disease states were derived from those applied during TA709 (Table 86), with unit costs (Table 85) obtained from the NHS National Cost Collection (2021-2022) or TA709 where relevant.[183]

Table 85. Unit costs for disease management and monitoring

Activity	Value	SE	References
Tumour marker test	£15.30	£3.06	IPG135[197], inflated to 2022/23 costs,[181] as in TA709[1]
Liver function test	£31.70	£6.34	IPG135[197], inflated to 2022/23 costs,[181] as in TA709[1]
CT scan	£146.34	£29.27	NHS National Cost Collection 2021/22[183], RD26Z: Computerised Tomography Scan of Three Areas, with Contrast, Imaging: Outpatient
MRI scan	£322.35	£64.47	NHS National Cost Collection 2021/22[183], RD05Z: Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast, Imaging: Outpatient
Consultation outpatient appointment	£210.25	£42.05	NHS National Cost Collection 2021/22[183], Service code: 370; medical oncology, weighted average of consultant and non-consultant led, non-admission face to face follow up visit
Best supportive care	£1,748.71	£349.74	Färkkilä (2015),[198] converted to GBP and inflated to 2022/23 costs,[181] as in TA709[1]

Abbreviations: CT, computed tomography; GBP, Great British pounds; NHS, National Health Service; MRI, magnetic resonance imaging; SE, standard error

Table 86. Resource per model cycle (28 days) per health state

	Value	SE	Reference
Progression-Free			
Tumour marker test	0.23	0.046	TA709[1], adjusted for 28-day model cycle length
Liver function test	1.15	0.23	TA709[1], adjusted for 28-day model cycle length

CT scan	0.3	0.06	TA709[1], adjusted for 28-day model cycle length
MRI scan	0.23	0.046	TA709[1], adjusted for 28-day model cycle length
Consultation outpatient appointment	2	0.4	TA709[1], adjusted for 28-day model cycle length
Progressed disease			
Best supportive care	0.92	0.184	TA709[1], adjusted for 28-day model cycle length

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SE, standard error

B.3.5.2.2 Terminal Care Costs

The base case analysis does not include an end-of-life cost, in line with TA709 and TA439. As the resource value in the progressed disease state includes palliative care costs, inclusion of end-of-life costs may result in double counting costs.

B.3.5.3 Adverse reaction unit costs and resource use

Unit costs per AE were based on prior TAs, the literature and National schedule of NHS costs (Table 87). To obtain costs per AE, unit costs per AE were multiplied with incidence of the event and were incurred in the first model cycle.

Table 87. Unit costs of AEs

Cost of grade 3-4 AE	Value	SE	Reference
Hepatitis	£621.75	£124.35	National schedule of NHS costs 2021/2022;[183] Weighted average of short stays for non-malignant hepatobiliary or pancreatic disorders without/single/multiple interventions (NHS HRG currency GC17A-GC17K)
Neutropenia	£770.53	£154.11	National schedule of NHS costs 2021/2022;[183] As per TA709[1]; Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions
Rash	£563.06	£112.61	National schedule of NHS costs 2021/2022;[183] Currency code JD07H Non-Elective Inpatient – Short-Stay, Skin Disorders without Interventions, with CC Score 6-9:
Diarrhoea	£1,044.17	£208.83	National schedule of NHS costs 2021/2022;[183] As per TA709;[1] Assumed that a typical patient will have two hospital admissions, corresponding to FD10M-Non- Malignant

			Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2 as a non-elective short-stay episode
Adrenal insufficiency	£9,082.82	£1,865.97	National schedule of NHS costs 2021/2022;[183] Based on Adrenal Procedures with CC Score 2+, Currency Code KA04A
Hyperthyroidism	£1,791.55	£358.31	National schedule of NHS costs 2021/2022;[183] Weighted average of all three combined non-surgical thyroid procedures with CC scores 0-1, 2-3, 4+(Currency code: KA07A, KA07B,KA07C) and costs of Oral delivery of radiotherapy for thyroid ablation (Currency code: RN51Z)[199]
Hypophysitis	£1,791.55	£358.31	National schedule of NHS costs 2021/2022;[183] Weighted average of all three combined non-surgical thyroid procedures with CC scores 0-1, 2-3, 4+(Currency code: KA07A, KA07B,KA07C) and costs of Oral delivery of radiotherapy for thyroid ablation (Currency code: RN51Z)[199]
Asthenia	£3,285.97	£657.19	National schedule of NHS costs 2021/2022;[183] As per TA709;[1] Assume equal to fatigue (Brown et al. 2013) WA17X code, no longer in use. Code used WH14C Other or Unspecified Neoplasm, without Interventions, with CC Score 2+
Decreased neutrophil count	£770.53	£154.11	National schedule of NHS costs 2021/2022;[183] Weighted average of CB02A:F, Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, Elective Inpatient [as per TA439][71]
Hypertension	£770.10	£158.74	National schedule of NHS costs 2021/2022;[183] As per TA709[1]
Pneumonia	£2,512.26	£516.10	National schedule of NHS costs 2021/2022;[183] As per TA709;[1] Weighted average of DZ11K:DZ11V, Lobar, Atypical or Viral Pneumonia, with Multiple Interventions/with Single Intervention/without Interventions, HRG

Abbreviations: AE, adverse event; CC, Charlson comorbidity; HRG, healthcare resource group; NHS, National Health Service

B.3.5.4 Miscellaneous unit costs and resource use

All costs and resource use has been detailed in previous sections.

B.3.6 Uncertainty

B.3.6.1 Overall survival outcomes

As noted in Section B.2.3.7, results for OS and other secondary endpoints were not tested in the interim CM8HW analysis, as per the hierarchical testing strategy pre-defined in the trial protocol. As noted, in Section B.2.10, immature OS data are commonly observed in appraisals of immunotherapies in mCRC, including TA716 and TA709. Due to the beneficial impact of immunotherapy on OS outcomes, few OS events are observed even with extended follow-up.[1,172] While this is beneficial for patients, it can prove challenging for robust data analysis.

Evidence from CM142 shows that NIVO + IPI is associated with sustained survival benefits with PFS and OS not reached after 64.2 months of follow-up. In addition, a strong association between PFS and OS in this cohort has been demonstrated, providing support for the use of PFS as a surrogate endpoint for OS in the absence of mature survival data.[123]

The economic model addresses this uncertainty using data from CM142 to inform PPS, which is assumed to be equivalent across therapies. Further, this uncertainty is addressed through scenario analyses.

B.3.6.2 Evidence in the dMMR/MSI-H subgroup

As outlined in Section B.1.3, dMMR/MSI-H mCRC comprises a small proportion of mCRC cases. Until recently, the majority of dMMR/MSI-H mCRC patients were treated with the limited number of treatments available for the overall mCRC population. As a result, evidence for comparator therapies was limited to the overall mCRC population, with few studies reporting dMMR/MSI-H status or outcomes in this population. More recently, therapies have been developed that aim to treat the dMMR/MSI-H subgroup (PEMBRO in the untreated setting and NIVO + IPI in the 2L+ setting).

Similarly, evidence generation has been restricted to the overall mCRC population previously, with limited studies assessing impact of dMMR/MSI-H status on prognosis, resource use or utilities. As a result, evidence gaps remain that have

been addressed using assumptions and inputs considered appropriate during previous NICE HTAs in dMMR/MSI-H.

B.3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base-case analysis inputs

Table 88. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Distribution	Reference to section
Female	0.538 (adults, Table 50); 0.643 (adolescents, Table 51); 0.5381 (weighted, Table 52)	Beta	B.3.2.1
Age at start (years)	60.9 (adults, Table 50); 14.5 (adolescents, Table 51); 60.85 (weighted, Table 52)	Normal	
Average weight	70.5 (adults, Table 50); 49.6 (adolescents, Table 51); 70.5 (weighted, Table 52)	Normal	
Mean body surface area (m2)	1.78 (adults, Table 50); 1.5 (adolescents, Table 51); 1.78 (weighted, Table 52)	Normal	
NIVO + IPI: PF-PD	Generalized gamma CM8HW data	Normal	B.3.3
PEMBRO: PF-PD	Generalized gamma based on ITC HR	Normal	
Chemotherapy: PF-PD	Generalized gamma CM-8HW data	Normal	
All treatments: PF-D	Background mortality	Normal	
All treatments: PD-D	Log-logistic CM142 PPS data	Normal	
Time on treatment	Kaplan-Meier data CM8HW	Normal	B.3.3.4
Resource use per health state: Progression-free	Table 86	Gamma	0
Resource use per health state: Progressed	Table 86	Gamma	
Initial therapy costs	Table 75, Table 79, Table 81	Gamma	B.3.5.1
Subsequent therapy costs	Table 84, Table 83	Gamma	
Drug administration costs	Table 73	Gamma	
Health state utilities	Table 72	Beta	B.3.4.5

Incidence of grade 3-4 AE	Table 65	Beta	B.3.3.5
Duration of AEs (in number of cycles)	Table 70	Normal	B.3.4.4
Disutility of grade 3-4 AE	Table 70	Beta	B.3.4.4
Cost of grade 3-4 AE	Table 87	Gamma	B.3.5.3

Abbreviations: AE, adverse event; IPI, ipilimumab; ITC, indirect treatment comparison; NIVO, nivolumab; PEMBRO, pembrolizumab; PD, progressed disease; PF, progression-free

B.3.7.2 Assumptions

Table 89. Assumptions applied within the economic model

Parameter	Assumption	Consistent with prior TTAs	Justification
Time horizon	Lifetime horizon	Yes	A lifetime horizon was used to capture all relevant cost and health effects. In the base case analysis, this was 40 years across all populations. An additional scenario analysis was undertaken for the adolescent population with longer time horizon to ensure that this reflected a true lifetime horizon.
PF-PD Transition probabilities of PEMBRO	These were based on an ITC assessing PFS for PEMBRO versus NIVO + IPI	N/A	As no direct comparison was available an indirect comparison was required. The treatment effect modifiers included were validated by clinical experts.
Fractional polynomial HR for PEMBRO versus NIVO + IPI	The base case includes a time-varying HR for the PEMBRO versus NIVO + IPI comparison	N/A	The time-varying hazard captures the fact that the PH assumption is not met.
PF-D and PD-D	The impact of treatment with NIVO + IPI versus PEMBRO and chemotherapy is only modelled through differences in the PF-PD transition	N/A	This is a conservative assumption when compared to PEMBRO, as this excludes all potential direct impacts on survival, including pre-progression survival.

Parameter	Assumption	Consistent with prior TTAs	Justification
PF-D	Background mortality is applied to describe pre-progression survival	N/A	The number of mortality events before progression in CM142 and CM8HW were extremely low but higher than background mortality. However, this can be considered conservative as it excludes a potential impact of treatment on pre-progression survival. An alternative is assessed in scenario analysis.
Utility values	Utility values in PF are assumed to differ between NIVO + IPI and chemotherapy	Yes	Aligned with TA709 and data derived from CM8HW
Utility values	Utility values in PD are assumed equal across all treatments.	Yes	Based on CM8HW estimates for NIVO + IPI and chemotherapy. For PEMBRO, equivalence to NIVO + IPI is a conservative and plausible assumption considering the safety profile of the treatment.
PEMBRO schedule	Patients receive PEMBRO every 6 weeks.	Yes	A conservative assumption as reduces administration costs
Treatment duration	PEMBRO is assumed equivalent to NIVO + IPI	N/A	This was a plausible assumption based on a comparison of duration of therapies between CM8HW and KN-177. Alternative assumptions would overestimate PEMBRO duration of treatment.
Subsequent therapy	Patients in the NIVO + IPI and PEMBRO arms are treated with chemotherapy (FOLFOX) in subsequent lines	No	Patients in the UK would be unlikely to receive subsequent immunotherapy. FOLFOX has the lowest acquisition cost and has been applied to be conservative.

Parameter	Assumption	Consistent with prior TTAs	Justification
Subsequent therapy	Patients in the chemotherapy arm are treated with NIVO + IPI in subsequent lines	No	Patients in the UK are likely to receive NIVO + IPI in the second-line setting if eligible
Patient monitoring	Patients visit the specialist once every 2 weeks	Yes	Aligns with prior submissions although frequency of follow-up visits may vary across countries.

Abbreviations: D, death; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; PD, progressed disease; PF, progression-free; PFS, progression-free survival

B.3.8 Base-case results

B.3.8.1 Base-case incremental cost-effectiveness analysis results

Base case analysis results are provided for the three populations of interest (adult, adolescent and weighted population). As can be seen, NIVO+IPI is considered to be a cost-effective use of NHS resources compared with comparator treatments across all populations of interest.

B.3.8.1.1 Adult population

The results of the base case analysis are summarised in s.

Table 90, with disaggregated results in Appendix J. In terms of comparator treatments, the model predicts mean undiscounted LLYs of [redacted] for PEMBRO and [redacted] for chemotherapy, correlating to discounted QALYs of [redacted] and [redacted], respectively. For chemotherapy, the majority of time was spent in progressed disease ([redacted] LLYs in PD versus [redacted] LYs in PFS), while patients spent longer progression-free for PEMBRO ([redacted] PFS versus [redacted] PD).

By comparison, it was predicted that the use of NIVO + IPI will result in an additional [redacted] discounted QALYs versus PEMBRO and an additional [redacted] discounted QALYs versus chemotherapy (total: [redacted] discounted QALYs).

Total discounted costs associated with NIVO + IPI (with PAS), accrued over the modelled time horizon, were predicted to be [redacted], which was lower than PEMBRO

(incremental: [redacted]) but had a higher cost versus chemotherapy (incremental: [redacted]). The resulting ICER estimates for NIVO + IPI were dominant versus PEMBRO, and £322 per QALY gained versus chemotherapy. Therefore, the base case ICERs are all substantially below a £30,000 per QALY willingness-to-pay threshold and NIVO + IPI can be considered a cost-effective use of NHS resources.

Table 90. Base-case results: adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£332

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 91. Base-case results: adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYG: life years gained; LYs: life years; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

B.3.8.1.2 Adolescent population

The results of the base case analysis are summarised in Table 92 and Table 93. Although PEMBRO is not licensed for use in adolescent patients with dMMR/MSI-H mCRC, we believe that adolescent patients are treated using adult guidelines. Hence results are also presented for NIVO + IPI versus both PEMBRO and chemotherapy.

In terms of comparator treatments, the model predicts mean undiscounted LYs of [redacted] for PEMBRO and [redacted] for chemotherapy, reflecting lower general population mortality in the population of interest. This correlated to discounted QALYs of [redacted] and [redacted], respectively. As a result, a large population remained alive at the end of the model time horizon: [redacted] in the NIVO + IPI arm, [redacted] in the PEMBRO arm and [redacted] in the chemotherapy arm.

By comparison, it was predicted that the use of NIVO + IPI will result in an additional [redacted] discounted QALYs versus PEMBRO and an additional [redacted] discounted QALYs versus chemotherapy (total: [redacted] discounted QALYs).

Total discounted costs associated with NIVO + IPI (with PAS), accrued over the modelled time horizon, were predicted to be [redacted], which was cost saving versus PEMBRO (incremental: [redacted]) but higher than chemotherapy (incremental: [redacted]), largely due to use of immunotherapies as a subsequent therapy. The resulting ICER estimates for NIVO + IPI were [redacted] Therefore, the base case ICERs are all substantially below a £30,000 per QALY willingness-to-pay threshold and NIVO + IPI can be considered a cost-effective use of NHS resources.

Table 92. Base-case results: adolescent population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,200

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 93. Base-case results: adolescent population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

B.3.8.1.3 Weighted population

The results of the base case analysis are summarised in Table 94 and Table 95. Outcomes were broadly aligned with the adult population, due to the high proportion of adult cases. The resulting ICER (with PAS) estimates for NIVO + IPI were

dominant versus PEMBRO and [redacted] per QALY gained versus chemotherapy. Therefore, the base case ICERs are all substantially below a £30,000 per QALY willingness-to-pay threshold and NIVO + IPI can be considered a cost-effective use of NHS resources.

Table 94. Base-case results: weighted population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYG: life years gained; LYs: life years; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 95. Base-case results: weighted population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYG: life years gained; LYs: life years; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

B.3.9 Exploring uncertainty

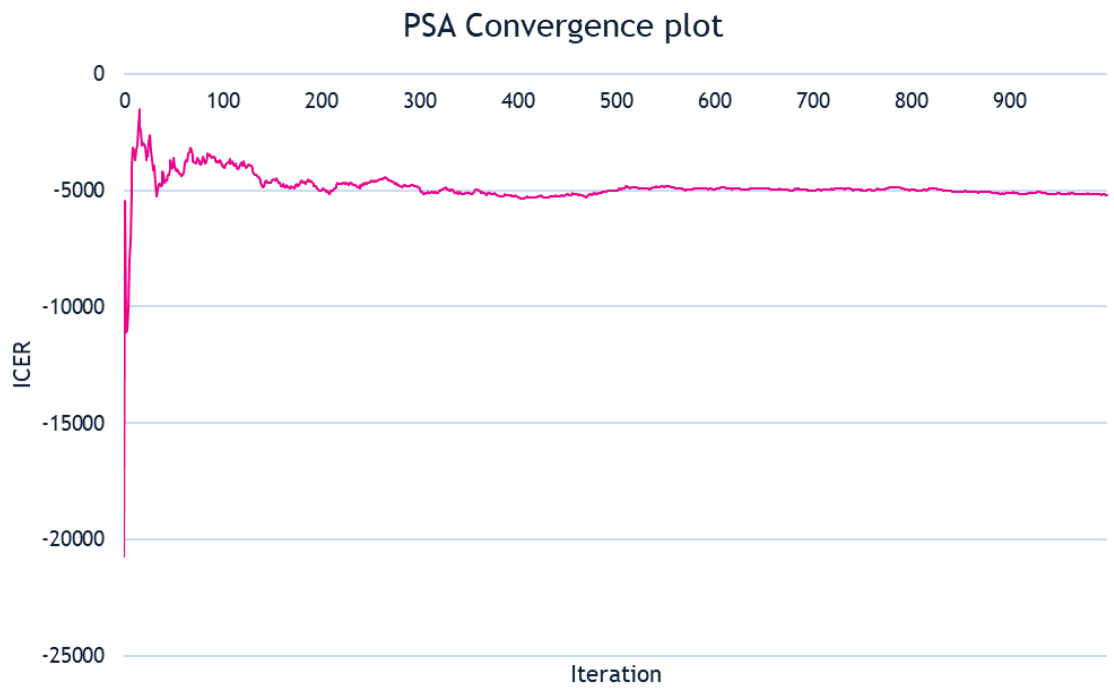
B.3.9.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the economic model samples values from distributions around the means of input parameters. Sampling utilises information of the mean and standard error of parameters to derive an estimated value using an appropriate distribution: costs, gamma; age and survival parameters, normal; utilities, probabilities and proportions, beta. These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters. The PSA is run separately for each comparator without applying a pre-set random number seed, leading to slight variations between runs even with identical model inputs.

Several inputs are derived from sources where it has not been possible to ascertain standard errors. To assess uncertainty surrounding these inputs, the standard error has been assumed to be 20% of the mean value for the purposes of the PSA.

As can be seen in Figure 48, convergence was reached after roughly 400 simulations. Therefore, running 500+ simulations gives a distribution of incremental results, and consequently, a robust estimate of the overall uncertainty surrounding cost-effectiveness results. Using the NMB approach, the probability of each treatment to be cost-effective at different levels of willingness-to-pay (WTP) per QALY is presented in the cost-effectiveness acceptability curve (CEAC).

Figure 48. PSA Convergence plot



Abbreviations: PSA, probabilistic sensitivity analysis

B.3.9.1.1 PSA results

PSA results are provided for the three populations of interest (adult, adolescent and weighted population), incorporating relevant NIVO + IPI PAS discounts. As can be seen, outcomes are comparable between the populations, underscoring the beneficial impact of NIVO + IPI across its licensed indication.

B.3.9.1.1.1 Adult population

Scatterplots for the base case analyses, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 49 (PEMBRO) and Figure 50 (chemotherapy), while cost-effectiveness acceptability curves (CEACs) are presented in Figure 51 (PEMBRO) and Figure 52 (chemotherapy). The PSA is run separately for each comparator without applying a pre-set random number seed, leading to slight variations between runs even with identical model inputs.

Based on these analyses, the probability that NIVO + IPI is cost-effective versus PEMBRO or chemotherapy is 100% and 100%, respectively, at a WTP threshold of £20,000/QALY gained and £30,000/QALY gained (Table 96).

Table 96. Probabilistic base-case results: adult population (with PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
Comparison of NIVO + IPI versus PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Comparison of NIVO + IPI versus chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 97. Probabilistic base-case results: adult population (no PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
Comparison of NIVO + IPI versus PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison of NIVO + IPI versus chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Figure 49. ICER scatterplot: NIVO + IPI versus pembrolizumab – adult population (with PAS)

Figure 50. ICER scatterplot: NIVO + IPI versus chemotherapy – adult population (with PAS)

Figure 51. Cost-effectiveness acceptability curve: NIVO + IPI versus pembrolizumab – adult population (with PAS)

Figure 52. Cost-effectiveness acceptability curve: NIVO + IPI versus chemotherapy – adult population (with PAS)

Figure 53. ICER scatterplot: NIVO + IPI versus pembrolizumab – adult population (no PAS)

Figure 54. ICER scatterplot: NIVO + IPI versus chemotherapy – adult population (no PAS)

Figure 55. Cost-effectiveness acceptability curve: NIVO + IPI versus pembrolizumab – adult population (no PAS)

Figure 56. Cost-effectiveness acceptability curve: NIVO + IPI versus chemotherapy – adult population (no PAS)

B.3.9.1.1.2 Adolescent population

Scatterplots for the base case analyses, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 57 (PEMBRO) and Figure 58 (chemotherapy), while cost-effectiveness acceptability curves (CEACs) are presented in Figure 59 (PEMBRO) and Figure 60 (chemotherapy). The PSA is run separately for each comparator without applying a pre-set random number seed, leading to slight variations between runs even with identical model inputs.

Based on these analyses, the probability that NIVO + IPI is cost-effective versus PEMBRO or chemotherapy is 100% and 100%, respectively, at a WTP threshold of £20,000/QALY gained and £30,000/QALY gained (Table 96).

Table 98. Probabilistic base-case results: adolescent population (with PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
Comparison of NIVO + IPI versus PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Comparison of NIVO + IPI versus chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£2,027

Costs and QALYs discounted; LYs undiscounted.

ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 99. Probabilistic base-case results: adolescent population (no PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
Comparison of NIVO + IPI versus PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]		
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison of NIVO + IPI versus chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Figure 57. ICER scatterplot: NIVO + IPI versus pembrolizumab - adolescent population (with PAS)

Figure 58. ICER scatterplot: NIVO + IPI versus chemotherapy - adolescent population (with PAS)

Figure 59. Cost-effectiveness acceptability curve: NIVO + IPI versus pembrolizumab - adolescent population (with PAS)

Figure 60. Cost-effectiveness acceptability curve: NIVO + IPI versus chemotherapy - adolescent population (with PAS)

Figure 61. ICER scatterplot: NIVO + IPI versus pembrolizumab - adolescent population (no PAS)

Figure 62. ICER scatterplot: NIVO + IPI versus chemotherapy - adolescent population (no PAS)

Figure 63. Cost-effectiveness acceptability curve: NIVO + IPI versus pembrolizumab - adolescent population (no PAS)

Figure 64. Cost-effectiveness acceptability curve: NIVO + IPI versus chemotherapy - adolescent population (no PAS)

B.3.9.1.1.3 Weighted population

Scatterplots for the base case analyses, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 65 (PEMBRO) and Figure 66 (chemotherapy), while cost-effectiveness acceptability curves (CEACs) are presented in Figure 67 (PEMBRO) and Figure 68 (chemotherapy). The PSA is run separately for each comparator without applying a pre-set random number seed, leading to slight variations between runs even with identical model inputs.

Based on these analyses, the probability that NIVO + IPI is cost-effective versus PEMBRO or chemotherapy is 100% and 100%, respectively, at a WTP threshold of £20,000/QALY gained and £30,000/QALY gained (Table 96).

Table 100. Probabilistic base-case results: weighted population (with PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
Comparison of NIVO + IPI versus PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Comparison of NIVO + IPI versus chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 101. Probabilistic base-case results: weighted population (no PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
Comparison of NIVO + IPI versus PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison of NIVO + IPI versus chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Figure 65. ICER scatterplot: NIVO + IPI versus pembrolizumab – weighted population (with PAS)

[redacted]

Figure 66. ICER scatterplot: NIVO + IPI versus chemotherapy – weighted population (with PAS)

Figure 67. Cost-effectiveness acceptability curve: NIVO + IPI versus pembrolizumab – weighted population (with PAS)

Figure 68. Cost-effectiveness acceptability curve: NIVO + IPI versus chemotherapy – weighted population (with PAS)

Figure 69. ICER scatterplot: NIVO + IPI versus pembrolizumab – weighted population (no PAS)

Figure 70. ICER scatterplot: NIVO + IPI versus chemotherapy – weighted population (no PAS)

Figure 71. Cost-effectiveness acceptability curve: NIVO + IPI versus pembrolizumab – weighted population (no PAS)

Figure 72. Cost-effectiveness acceptability curve: NIVO + IPI versus chemotherapy – weighted population (no PAS)

B.3.9.2 Deterministic sensitivity analysis

The deterministic sensitivity analysis (DSA) involves varying one parameter at a time and assessing the subsequent impact on the incremental costs, incremental QALYs and ICER. Each parameter is allocated a 'low' value and a 'high' value; unless otherwise stated, the low value is the lower bound of the 95% CI and the high value is the upper bound of the 95% CI (Table 102). By adjusting each parameter one at a time, the DSA assesses the impact of uncertainty around individual input parameters on the model outcomes. Results are presented in tables and tornado plots, which clearly present the parameters that have the greatest effect on the relevant model outcomes. The most influential parameters are presented.

Table 102. Deterministic sensitivity analysis settings

Parameter		Unit	Base case value	Lower limit	Upper limit
Model settings	Cost discounting	%	3.5	0	6
	Effects discounting		3.5	0	6
Population settings	Age of population used	Years	60.9	48.72	73.08
	Percentage female	%	53.8	0	100
Mean time in progressed disease	Mean time in progressed disease state (PEMBRO and NIVO + IPI)	Months	1,271.07	772.82	1,769.32
Time on treatment	Chemotherapy - Mean time on subsequent treatment		20.16	13.05	28.80

	NIVO+IPI - Mean time on subsequent treatment		48.27	31.23	68.94
Resource use	Tumour marker test	Use per cycle	0.23	0.149	0.329
	Liver function test		1.15	0.744	1.643
	CT scan		0.3	0.194	0.429
	MRI scan		0.23	0.149	0.329
	Consultation outpatient appointment		2	1.294	2.86
	Best supportive care		0.92	0.595	1.31
Resource costs	Simple IV administration	£	286.71	190.79	421.11
	Complex IV administration		474.94	315.76	696.94
	Tumour marker test		15.3	9.90	21.85
	Liver function test		31.7	20.51	45.28
	CT scan		164.35	106.36	234.76
	MRI scan		249.61	161.53	356.54
	Consultation appointment		211.6	136.94	302.25
	Best supportive care		1,748.71	1,131.67	2,497.86
AE costs	Hepatitis	£	621.75	497.40	746.1
	Neutropenia		770.53	616.42	924.64
	Rash		5,63.06	450.45	675.67
	Diarrhoea/colitis		1,044.17	835.34	1,253.00
	Adrenal insufficiency		9,082.82	7,266.26	10,899.38
	Hyperthyroidism		1,791.55	1,433.24	2,149.86
	Hypophysitis		1,791.55	1,433.24	2,149.86
	Asthenia		3,285.97	2,628.78	3,943.16
	Decreased neutrophil count		770.53	616.42	924.64
	Hypertension		770.1	616.08	924.12
	Pneumonia		2,512.26	2,009.81	3,014.71
Utilities	Progression free utility	Utility	0.76	0.735	0.784
	Progressed disease utility		0.733	0.695	0.769

Abbreviations: AE, adverse event; CT, computed tomography; IPI, ipilimumab; IV, intravenous; MRI, magnetic resonance imaging; NIVO, nivolumab; PEMBRO, pembrolizumab

B.3.9.2.1 Deterministic sensitivity analysis results

Base case analysis results are provided for the three populations of interest (adult, adolescent and weighted population), incorporating relevant NIVO + IPI PAS discounts.

B.3.9.2.1.1 Adult population

Results of the deterministic sensitivity analysis are presented in Figure 73 (PEMBRO) and Figure 74 (chemotherapy) and demonstrate the impact of specific

parameters on ICER estimates. In all scenarios, the ICER for NIVO + IPI versus comparators remained below the £30,000 per QALY willingness-to-pay threshold.

Plausible scenarios have been investigated further in Section B.3.9.3, in order to assess the impact of the uncertainty in the analysis.

B.3.9.2.1.2 Adolescent population

Results of the deterministic sensitivity analysis are presented in Figure 77 (PEMBRO) and Figure 78 (chemotherapy) and demonstrate the impact of specific parameters on ICER estimates. In all scenarios, the ICER for NIVO + IPI versus comparators remained below the £30,000 per QALY willingness-to-pay threshold.

B.3.9.2.1.3 Weighted population

Results of the deterministic sensitivity analysis are presented in Figure 81 (PEMBRO) and Figure 82 (chemotherapy) and demonstrate the impact of specific parameters on ICER estimates. In all scenarios, the ICER for NIVO + IPI versus comparators remained below the £30,000 per QALY willingness-to-pay threshold.

Figure 73. DSA outcomes: NIVO + IPI versus pembrolizumab – adult population (with PAS)

Abbreviations: CT, computed tomography; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab

Figure 74. DSA outcomes: NIVO + IPI versus chemotherapy – adult population (with PAS)

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

Figure 75. DSA outcomes: NIVO + IPI versus pembrolizumab – adult population (no PAS)

Abbreviations: CT, computed tomography; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab

Figure 76. DSA outcomes: NIVO + IPI versus chemotherapy – adult population (no PAS)

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

Figure 77. DSA outcomes: NIVO + IPI versus pembrolizumab – adolescent population (with PAS)

Abbreviations: CT, computed tomography; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab

Figure 78. DSA outcomes: NIVO + IPI versus chemotherapy – adolescent population (with PAS)

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

Figure 79. DSA outcomes: NIVO + IPI versus pembrolizumab – adolescent population (no PAS)

Abbreviations: CT, computed tomography; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab

Figure 80. DSA outcomes: NIVO + IPI versus chemotherapy – adolescent population (no PAS)

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

Figure 81. DSA outcomes: NIVO + IPI versus pembrolizumab – weighted population (with PAS)

Abbreviations: CT, computed tomography; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab

Figure 82. DSA outcomes: NIVO + IPI versus chemotherapy – weighted population (with PAS)

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

Figure 83. DSA outcomes: NIVO + IPI versus pembrolizumab – weighted population (no PAS)

Abbreviations: CT, computed tomography; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab

Figure 84. DSA outcomes: NIVO + IPI versus chemotherapy – weighted population (no PAS)

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

B.3.9.3 Scenario and one-way sensitivity analysis

As outlined in Sections B.3.8.1 (base case analysis results), B.3.9.1.1 (PSA results) and B.3.9.2.1 (DSA results), outcomes for the populations of interest remain relatively comparable. As a result, scenario and one-way sensitivity analyses have been undertaken using the adult population only, unless otherwise specified. Outcomes can be expected to be comparable for the adolescent and weighted populations.

B.3.9.3.1 Analysis of OS uncertainty

B.3.9.3.1.1 Alternative economic model time horizon

As previously discussed, there are limitations to the available evidence, particularly for OS data, within the economic model that have been addressed through plausible assumptions and scenario analysis. However, the initial five-year modelled period can be considered more robust, as it requires fewer assumptions and can be validated using observed trial data. Further, at this time point, first line treatment has already ceased and economic model clinical outputs can be validated against observed values from clinical trials, reducing uncertainty. This scenario analysis restricts the model time horizon to five years.

Results are provided in Table 103. As can be seen, total LYs and QALYs are decreased across all modelled treatment arms; however, NIVO + IPI maintains a benefit over PEMBRO and chemotherapy. First-line treatment costs remain relatively unchanged by decreasing the time horizon, but resource use and subsequent treatment costs are lower than the base case analysis. This is particularly impactful versus chemotherapy, where incremental costs are slightly increased. However, ICERs remain below a £30,000/QALY willingness-to-pay threshold.

Table 103. Scenario analysis: five-year model time horizon - adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	£13,855

Costs and QALYs discounted; LYs undiscounted
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.9.3.1.2 Alternative source for PF-D transition

As outlined in Section B.3.3.2, there are limited data sources that can be used to estimate the PF-D transition. While general population mortality is applied in the base case analysis, CM142 PrePS data were available and have been applied as a scenario analysis.

There was a total of 164 patients used to inform this analysis (Cohort 2 [2L+ NIVO + IPI]: 119 patients; Cohort 3 [1L NIVO+IPI]: 45 patients), all of which received NIVO + IPI (Figure 85). The median time to death was not reached and the one-year survival probability was [redacted] (95% CI: [redacted]).

Figure 85. CM142 cohorts 2 and 3 pre-progression survival Kaplan-Meier data

As previously mentioned, there were few events so that the data can be considered extremely immature and should be viewed with caution, as evidenced by Figure 86.

As previously described for the TTP survival analysis, the best model fit was selected based on the model selection algorithm outlined in Palmer et al. (2023)[186] as well as via statistical tests such as AIC. The lognormal model is recommended based on low AIC value and plausible long-term extrapolation. For this scenario analysis, the economic model applies this data in addition to general population mortality.

Figure 86. CM142 cohort 2 (2L+ NIVO + IPI) and 3 (1L NIVO + IPI) PrePS standard parametric fits beyond trial period

Results are provided in Table 104. Total LYs and QALYs are decreased across all modelled treatment arms due to increased deaths from the progression-free state. However, this results in lower resource use for NIVO + IPI and PEMBRO, so that ICERs are relatively unchanged versus PEMBRO and are dominant versus chemotherapy.

Table 104. Scenario analysis: CM142 for PF-D transition - adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	Dominant

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.9.3.2 Analysis of uncertainty in long-term comparative effectiveness

B.3.9.3.2.1 Alternative ITC approaches to inform PEMBRO PF-PD transition

Three ITC approaches were undertaken to inform the comparison of NIVO + IPI and PEMBRO: fractional polynomial NMA; anchored or unanchored MAIC; and constant HR NMA. The fractional polynomial NMA was used in the base case analysis. Alternative approaches have been assessed in scenario analysis.

As shown in

Table 105, across all ITC approaches, NIVO+IPI was predicted to be cost saving compared with PEMBRO. However, the unanchored MAIC and constant HR NMA predicted higher LYs and QALYs for PEMBRO while the anchored MAIC provided lower LYs and QALYs. Despite this, the ICER for NIVO+IPI remains dominant across all ITC approaches, demonstrating that NIVO+IPI offers a cost-effective use of NHS resources.

Table 105. Scenario analysis: alternative ITC approaches to inform PEMBRO PF-PD transition - adult population (with PAS)

	NIVO + IPI	PEMBRO			
		Base case	Anchored MAIC	Unanchored MAIC	Constant HR NMA
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	Dominant	Dominant	Dominant

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.9.3.2.2 Alternative TTP extrapolations for NIVO + IPI

Survival modelling using long-term extrapolation of parametric functions is subject to considerable uncertainty despite efforts to robustly and transparently provide survival curves that best represent patients in clinical practice. In order to assess the impact

of alternative TTP parametric extrapolations on the cost-effectiveness of NIVO+IPI, survival curves described in the survival analysis report (Appendix O) have been applied within the model as scenario analyses.

This analysis should be viewed within the context of identifying the most appropriate survival extrapolation, as detailed in Section B.3.3.1. All extrapolations have been assessed for completeness. However, it should be noted that several of these extrapolations are not considered appropriate. Clinically implausible fits are presented in grey italics.

As shown in Table 106, across all extrapolations, NIVO+IPI is associated with improved QALYs compared with PEMBRO and chemotherapy and is cost-saving compared with PEMBRO across all TTP extrapolations, yielding dominant ICERs compared with PEMBRO. Although NIVO+IPI is associated with marginally higher costs compared with chemotherapy, this is offset by improved QALYs so ICERs indicate that NIVO+IPI provides an acceptable use of NHS resources.

Table 106. Scenario analysis: alternative NIVO + IPI TTP extrapolations - adult population (with PAS)

NIVO + IPI TTP extrapolations (ordered by AIC)	PEMBRO			Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
Generalised Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£332
Lognormal	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£268
Log-logistic	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£192
Gompertz*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£562
Weibull	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£337
Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£414
Exponential*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£144

*Clinically implausible extrapolations, as outlined in Section B.3.3.1.1.1.
Abbreviations: AIC, Akaike information criterion; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TTP, time to progression

B.3.9.3.2.3 Alternative TTP extrapolations for chemotherapy

As outlined above for NIVO + IPI, chemotherapy TTP parametric extrapolations described in the survival analysis report (Appendix O) have been applied within the model as scenario analyses.

This analysis should be viewed within the context of identifying the most appropriate survival extrapolation, as detailed in Section B.3.3.1. All extrapolations have been assessed for completeness.

Across all extrapolations for alternative chemotherapy, NIVO+IPI is associated with higher costs than chemotherapy; however, improvements in QALYs result in ICERs that are substantially below a £30,000 per QALY willingness-to-pay threshold.

Table 107. Scenario analysis: alternative chemotherapy extrapolations - adult population (with PAS)

Chemotherapy TTP extrapolation (ordered by AIC)	NIVO + IPI versus Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
Lognormal	[redacted]	[redacted]	£1,388
Generalised Gamma	[redacted]	[redacted]	£322
Log-logistic	[redacted]	[redacted]	£1,328
Gamma	[redacted]	[redacted]	£1,900
Exponential	[redacted]	[redacted]	£1,645
Weibull	[redacted]	[redacted]	£1,840
Gompertz	[redacted]	[redacted]	£378

Abbreviations: AIC, Akaike information criterion; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TTP, time to progression

B.3.9.3.2.4 Comparison versus panitumumab + FOLFOX

Although direct trial evidence is not available for NIVO+IPI versus panitumumab, direct evidence is available for NIVO+IPI versus cetuximab-based therapy, which NICE has previously concluded has comparable efficacy to panitumumab-based therapy (TA709). Despite this conclusion, an ITC scenario analysis has been conducted to inform a comparison of NIVO+IPI versus panitumumab.

Table 108 reports model outcomes for a scenario using outputs from the ITC described in SectionB.2.7.2.2.3. As can be seen, LYs and QALYs are broadly aligned with the overall chemotherapy arm from the base case analysis. However, costs are increased, so that NIVO + IPI has become cost saving. As a result, NIVO + IPI is dominant in this scenario.

Table 108. Scenario analysis: NIVO + IPI versus panitumumab + FOLFOX - adult population (with PAS)

	NIVO + IPI	Panitumumab + FOLFOX
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years

B.3.9.3.2.5 Extended model time horizon for adolescent population

In the base case analysis, the model time horizon is 40 years. However, the adolescent population base case analysis uses a baseline age of 14.5 years, so that patients are modelled to aged 54.5 years. This scenario analysis models patients through to 100 years of age (i.e., lifetime horizon).

Table 109 provides an overview of outcomes. As can be seen, survival is slightly extended versus the base case analysis across all treatment arms. As a result, costs are also slightly increased, resulting in minor changes in the ICER versus the base case analysis.

Table 109. Scenario analysis: extended model time horizon – adolescent population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	£332	£3,436

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; LY, life years; NIVO, nivolumab; PEMBRO, pembrolizumab; QALY, quality adjusted life year

B.3.9.3.3 Analysis of uncertainty in subsequent treatment for chemotherapy arm

B.3.9.3.3.1 Alternative post-progression cost in chemotherapy arm

The base case analysis assumes that patients receiving chemotherapy in the first-line setting will receive NIVO + IPI in the second-line setting. However, some patients may not be eligible for second-line NIVO+IPI and may receive chemotherapy. This scenario aligns subsequent treatment in the chemotherapy arm with subsequent treatment in the NIVO + IPI and PEMBRO arms, applying equivalent costs.

Table 110 provides an overview of outcomes from this scenario analysis. As can be expected, LY and QALY outcomes remain consistent with the base case analysis. However, costs within the chemotherapy arm have decreased, resulting in an increased ICER (£15,281/QALY gained). However, this remains below a £30,000/QALY willingness to pay threshold, so that NIVO + IPI can still be considered a cost-effective use of NHS resources.

Table 110. Scenario analysis: alternative post-progression survival in chemotherapy arm - adult population (with PAS)

	NIVO + IPI	Chemotherapy
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	£15,281

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years

B.3.9.3.4 Analysis of uncertainty in utility values

B.3.9.3.4.1 Alternative health state utility values

The economic model uses treatment-specific progression free utility data, which is appropriate in the context of the statistically significant difference between the NIVO

+ IPI and chemotherapy arms during the utility analysis. However, a scenario analysis has assessed alternative health state utility values, as outlined in Table 111.

Table 111. Overall utilities from CM8HW compared with previous CRC HTAs

		Progression-free	Progressed
CM8HW	Overall	[redacted]	[redacted]
TA709 (KN-177)	PEMBRO	0.843	0.730
	Chemotherapy	0.787	0.730
TA439	Cetuximab, panitumumab and chemotherapy	0.767	0.64

Abbreviations: CRC, colorectal cancer; HTA, health technology assessment; PEMBRO, pembrolizumab

Table 112 provides an overview of outcomes. Using utilities from different sources has minimal effect on ICERs compared with the base case analysis; NIVO+IPI remains dominant compared with PEMBRO across all alternative utilities and has an ICER that represents a cost-effective use of NHS resources compared with chemotherapy.

Table 112. Scenario analysis: application of alternative utilities – adult population (with PAS)

	CM8HW overall utilities		TA709 utilities		TA439 UTILITIES	
	PEMBRO	Chemo	PEMBRO	Chemo	PEMBRO	Chemo
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	Dominant	£389	Dominant	£310	Dominant	£375

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.9.3.5 Alternative cost and healthcare resource use

B.3.9.3.5.1 Alternative chemotherapy cost composition

The base case analysis applied chemotherapy costs that were weighted according to the proportion of patients receiving each regimen. This scenario analysis assessed the impact of alternative cost composition but assessing high-cost chemotherapy composition (100% panitumumab plus FOLFIRI; 100% cetuximab plus FOLFIRI) and a low-cost chemotherapy composition (100% FOLFOX).

Table 113 provides an overview of results. As expected, NIVO+IPI is cost saving compared with FOLFIRI + panitumumab and FOLFIRI + cetuximab with a dominant ICER. NIVO+IPI was associated with a higher cost than FOLFOX, but still yielded an ICER that suggests it is a cost-effective use of NHS resources.

Table 113. Scenario analysis: alternative chemotherapy costs – adult population (with PAS)

Chemotherapy composition	NIVO + IPI versus Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER versus NIVO + IPI (£/ QALY)
Panitumumab plus FOLFIRI	[redacted]	[redacted]	Dominant
Cetuximab plus FOLFIRI	[redacted]	[redacted]	Dominant
FOLFOX	[redacted]	[redacted]	£1,063

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab

B.3.10 Subgroup analysis

B.3.10.1 Analysis of centrally confirmed dMMR/MSI-H CheckMate 8HW subgroup

The base case analysis applies evidence from the CM8HW ITT population. However, the CM8HW included a subgroup of patients with centrally confirmed dMMR/MSI-H status. This scenario analysis reflects this subgroup of patients.

Table 114 provides an overview of results. LYs and QALYs are increased across all treatment arms so that incremental QALYs for NIVO + IPI versus comparators remained comparable with the base case analysis. However, this has a consequent increase in resource use and subsequent treatment costs that improve cost savings

for NIVO + IPI versus comparators. As a result, NIVO + IPI is dominant versus both PEMBRO and chemotherapy.

Table 114. Subgroup analysis: centrally confirmed dMMR/MSI-H CM8HW – adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	Dominant

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.11 Summary of sensitivity analysis results

A large number of sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model. In the deterministic analysis, NIVO + IPI was cost-effective against all scenarios at a WTP threshold of £30,000/QALY. Similarly, in the PSA, the probability that NIVO + IPI is cost-effective versus PEMBRO is 100% and versus chemotherapy is 100% at a WTP threshold of £20,000/QALY gained and £30,000/QALY gained.

Plausible alternative inputs and assumptions were assessed as scenario analyses within Section B.3.9.3, as depicted in Figure 87. Reflecting the PSA and deterministic sensitivity analysis, all of the ICERs remain below the £30,000/QALY threshold.

Figure 87. Scenario analysis: overview of all scenarios

Abbreviations: PEMBRO, pembrolizumab; QALY, quality-adjusted life-years

B.3.12 Benefits not captured in the QALY calculation

As stated by the Bowel Cancer UK during engagement for TA709, dMMR/MSI-H is a rare subtype of CRC with limited treatment options available. Although PEMBRO has been recommended in patients who were previously untreated, NIVO + IPI provides an efficacious alternative to PEMBRO with a different mechanism of action, thus increasing therapeutic diversity. Additionally, NIVO + PEMBRO would be the first immune-oncology therapy for adolescent patients with dMMR/MSI-H mCRC to be assessed by NICE.

NIVO + IPI is a highly innovative, targeted immuno-oncology therapy with a unique mechanism of action and published data describing the beneficial impact of therapy in terms of efficacy and safety. The synergistic mechanism of action, targeting multiple receptors at once, has the potential to increase response and may be preferable to treatment that only targets one receptor.

Further, in the context of the clinical benefits observed in CM142 and CM8HW, the use of NIVO + IPI may result in potential substantial HRQoL benefits for patients' caregivers that are not reflected in the QALY calculation.

For dMMR/MSI-H mCRC, there are additional challenges to adequately capturing benefits. There are fewer patients to inform collection of robust, nuanced HRQoL data compared with the overall mCRC population. Additional, historical alternatives have poorer efficacy so that a robust, nuanced QALY calculation is challenging, both practically and ethically.

B.3.13 Validation

A technical review of the cost-effectiveness model was conducted by an independent economist. Further, the relevance of the model structure and assumptions were validated through consultation with UK clinicians. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

In general, where no evidence has been identified, simple assumptions have been made based on independent sources, such as published literature, CRC guidelines or previous NICE appraisals in the field of CRC. These assumptions were then assessed for clinical plausibility; uncertainty has been characterised through the use of sensitivity analyses. Extensive sensitivity analyses were then undertaken, and all ICERs remain below a £30,000/QALY threshold.

B.3.13.1 Validation of cost-effectiveness analysis

B.3.13.1.1 Validation to observed KEYNOTE-177 outcomes

Long-term survival outcomes are available from KN-177 and can be used to assess the clinical plausibility of economic model outcomes.

B.3.13.1.1.1.1 Chemotherapy arm

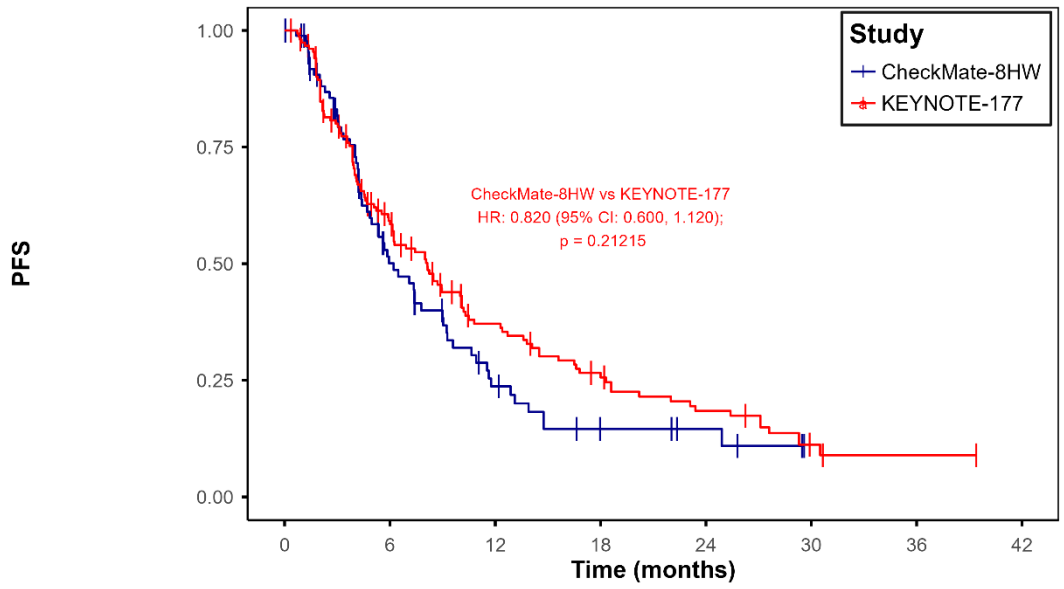
Table 115 demonstrates that OS outcomes for chemotherapy are initially higher in the economic model than in KN-177. However, by year five, OS is lower in the economic model than in KN-177.

This can be expected, as chemotherapy PFS outcomes for CheckMate 8HW are numerically lower than for KEYNOTE-177, although not statistically significant

(Figure 88). The reasons for this are not entirely clear, as outcomes are aligned by 24 months. One possible rationale is slightly higher bevacizumab usage in KN-177, although this has limited impact on the comparison of NIVO + IPI versus chemotherapy, as shown in Table 31. Additionally, this difference may be a result of crossover to NIVO + IPI in CM8HW. However, results for PFS per BICR using the EMA definition, which does not apply censoring at subsequent anti-cancer therapy initiation, were consistent with the primary analysis ([redacted]).[114] As such, neither rationale would impact on the understanding of NIVO + IPI versus chemotherapy.

As the economic model applies CM8HW TTP to inform the PF-PD transition for the chemotherapy arm, it can be expected that increased progression will increase movement to the progressed disease state and hence OS. Further, pre-progression LYs for the chemotherapy arm are broadly aligned with output from the TA709 economic model, as outlined in Table 117. Overall mean LYs are higher than the TA709 economic model, due to inclusion of NIVO + IPI as a second-line treatment.

Figure 88. Comparison of chemotherapy PFS for CM8HW and KN-177



NAR (Cumulative Events)

CheckMate-8HW	101 (0)	35 (39)	14 (56)	6 (61)	4 (61)	0 (62)	0 (62)	0 (62)
KEYNOTE-177	154 (0)	81 (60)	43 (88)	27 (101)	18 (108)	5 (114)	3 (115)	0 (115)

Abbreviations: PFS, progression-free survival

B.3.13.1.1.1.2 Pembrolizumab arm

Survival outcomes for pembrolizumab are broadly aligned between KN-177 and the economic model, although slightly lower by year 5. However, all values are within a plausible range.

Table 115. Comparison of economic model outcomes and KN-177

		1 year OS, %	3-year OS, %	5-year OS, %
Chemotherapy	Base case	[redacted]	[redacted]	[redacted]
	KN-177[187,200]	74.0	50.3	44.2
Pembrolizumab	Base case (fractional polynomial)	[redacted]	[redacted]	[redacted]
	Anchored MAIC	[redacted]	[redacted]	[redacted]
	Unanchored MAIC	[redacted]	[redacted]	[redacted]
	Constant HR	[redacted]	[redacted]	[redacted]
	KN-177[187,200]	77.8	61.4	54.8

Abbreviations: HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival

B.3.13.1.2 Validation of NIVO + IPI outcomes versus CheckMate 142 Cohort 3 (1L NIVO + IPI) and Cohort 2 (2L+ NIVO + IPI)

NIVO + IPI survival outcomes are available from CM142 Cohort 3 (1L NIVO + IPI) and Cohort 2 (2L+ NIVO + IPI). As a result, these can be used to assess the clinical plausibility of economic model outcomes. Table 116 shows that the economic model initially predicts OS higher than that observed in clinical trial. However, by year two, survival outcomes from the economic model are broadly aligned with CM142 cohort 3 (1L NIVO + IPI) and Cohort 2 (2L+ NIVO + IPI).

Table 116. Comparison of economic model outcomes and CM142 cohort 3 (1L NIVO + IPI)

	Economic model	CM142 cohort 3 (1L NIVO + IPI)	CM142 cohort 2 (2L+ NIVO + IPI
1-year OS, %	[redacted]	84.1	84.9
2-year OS, %	[redacted]	79.4	74.8
5-year OS, %	[redacted]	67	67.9

Abbreviations: OS, overall survival

B.3.13.1.3 Validation to TA709 outcomes

TA709 reports survival outcomes for PEMBRO and key comparators.[1] Table 117 provides a comparison of survival outcomes from TA709 versus the economic model. As can be seen, predicted pre-progression LYs are broadly comparable with values output from TA709. However, progressed disease LYs are impacted by the use of immunotherapies as a subsequent treatment, particularly for chemotherapy.

Table 117. Comparison of survival outcomes between TA709[125] and current economic model

Comparator	Appraisal	Total LYs	Progression-free LYs	Progressed disease LYs
Pembrolizumab	TA709	6.93	4.56	2.37
	Current	[redacted]	[redacted]	[redacted]
SoC/CAPOX	TA709	3.78	1.21	2.57
	Current	[redacted]	[redacted]	[redacted]
Panitumumab+ FOLFOX	TA709	4.10	1.55	2.55
	Current			

Abbreviations: CAPOX: capecitabine, oxaliplatin; FOLFOX: fluorouracil, folinic acid, oxaliplatin; LY: life year; SOC: standard of care.

B.3.14 Interpretation and conclusions of economic evidence

Base case analysis

- Use of NIVO + IPI results in incremental QALYs of [redacted] versus PEMBRO and [redacted] versus chemotherapy.
- After accounting for a PAS, discounted incremental costs were estimated to be [redacted] versus chemotherapy and cost saving versus pembrolizumab ([redacted]).
- The resultant ICER was £332 per QALY versus chemotherapy, which is considered to be cost-effective at a willingness-to-pay threshold of £30,000 per QALY.
- NIVO + IPI was considered to be dominant versus PEMBRO.

Sensitivity analysis

- In the probabilistic sensitivity analysis and deterministic sensitivity analysis, NIVO + IPI was cost-effective in all scenarios at a willingness-to-pay threshold of £30,000 per QALY.

- Extensive scenario analyses and one-way sensitivity analyses were undertaken, reflecting the assumptions required to undertake plausible, robust and transparent base case analysis. Within these scenario analyses, all of the ICERs remain below the £30,000 per QALY threshold.
- Therefore, NIVO + IPI can be considered a cost-effective use of NHS resources.

The population included in the economic evaluation was consistent with the UK population eligible for NIVO + IPI as per the anticipated licence. Clinical efficacy was derived from CM8HW, which reflects the adult patient population of interest in the UK. Additional analyses used clinical efficacy from CM8HW applied in an adolescent population.

The analysis is directly applicable to clinical practice in England:

- As outlined in B.2.10.3, the patient population of CM8HW is reflective of UK patients with dMMR/MSI-H mCRC.
- The comparators available within the model reflect UK clinical practice and the NICE final scope.[184]
- The resource utilisation and unit costs are reflective of UK clinical practice and were derived from the National schedule of NHS costs and aligned with previous NICE mCRC HTA preferences.
- A pharmacokinetic simulation study concluded that the exposure of the proposed dosing regimen for both NIVO and IPI in adolescents is expected to result in comparable benefits and risks to those in adults.

Further, the analysis performed makes use of the best available evidence to inform the model. Although there are several areas of uncertainty, extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs. Direct head-to-head data were not available for NIVO + IPI versus PEMBRO; however, several ITC methodologies have been employed to explore the uncertainty

around indirect estimates of comparative effectiveness, all of which have been applied in the economic model.

A number of patients in the chemotherapy arm crossed over to receive NIVO + IPI as a subsequent treatment. However, these patients did not impact on the economic model as an independent source of efficacy was applied to inform PPS. Further, no crossover analysis has been undertaken, as results for PFS per BICR using the EMA definition, which does not apply censoring at subsequent anti-cancer therapy initiation, were consistent with the primary analysis ([redacted]).[114]

In summary, availability of NIVO + IPI would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need. The adoption of NIVO + IPI in this therapeutic indication in NHS England would represent a further, significant advance in the management of this life-threatening condition and would be a cost-effective use of NHS resources.

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B.5 Appendices

In line with the user guide for company evidence submission template, appendices start at C, because document A is the submission summary and document B is the main submission.

Appendix number	Appendix Title	Location
C	Nivolumab draft SmPC reflecting the EMA submission NB: A version of the UKPAR is not yet available	Provided as a separate document
D	Identification, selection and synthesis of clinical evidence: systematic literature review report	Provided as a separate document
E	Subgroup analysis	Provided in the main body of the report
F	Adverse reactions	Provided in the main body of the report
G	Published cost-effectiveness studies: systematic literature review	Provided as a separate document
H	Health-related quality-of-life studies: systematic literature review	Provided as a separate document
I	Cost and healthcare resource identification:	Provided as a separate document
J	Clinical outcomes and disaggregated results from the model	Provided below
K	Price details of treatments included in the submission	Provided below
L	Checklist of confidential information	Provided as a separate document
M	ITC feasibility assessment	Provided as a separate document
N1	ITC report – fractional polynomial	Provided as a separate document
N2	ITC report – anchored MAIC and constant hazards NMA	Provided as a separate document
N3	ITC report – unanchored MAIC	Provided as a separate document
O	Survival analysis report	Provided as a separate document
P	Utility report	Provided as a separate document

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 Clinical outcomes from the model

Clinical outcomes are summarised in Table 118 (adult population), Table 119 (adolescent population) and Table 120 (weighted population). Comparison with outcomes in clinical trials are provided in Section B.3.13.1.

J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Clinical outcomes are summarised in Table 118 (adult population), Table 119 (adolescent population) and Table 120 (weighted population).

Table 118. Base case analysis results: disaggregated outcomes for adult population (with PAS)

	NIVO + IPI	Pembrolizumab	Chemotherapy
Clinical outcomes			
QALYs (discounted)	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Disutility of grade 3-4 AE	[redacted]	[redacted]	[redacted]
Life years (undiscounted)	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Cost outcomes (discounted)			
Total Costs	[redacted]	[redacted]	[redacted]
Treatment-related costs	[redacted]	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]
Total resource use	[redacted]	[redacted]	[redacted]
Resource use	[redacted]	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; IPI, ipilimumab; NIVO, nivolumab; QALY, quality-adjusted life-year

Table 119. Base case analysis results: disaggregated outcomes for adolescent population (with PAS)

	NIVO + IPI	Pembrolizumab	Chemotherapy
Clinical outcomes			
QALYs (discounted)	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Disutility of grade 3-4 AE	[redacted]	[redacted]	[redacted]
Life years (undiscounted)	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Cost outcomes (discounted)			
Total Costs	[redacted]	[redacted]	[redacted]
Treatment-related costs	[redacted]	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]
Total resource use	[redacted]	[redacted]	[redacted]
Resource use	[redacted]	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; IPI, ipilimumab; NIVO, nivolumab; QALY, quality-adjusted life-year

Table 120. Base case analysis results: disaggregated outcomes for weighted population (with PAS)

	NIVO + IPI	Pembrolizumab	Chemotherapy
Clinical outcomes			
QALYs (discounted)	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Disutility of grade 3-4 AE	[redacted]	[redacted]	[redacted]
Life years (undiscounted)	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Cost outcomes (discounted)			
Total Costs	[redacted]	[redacted]	[redacted]
Treatment-related costs	[redacted]	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]
Total resource use	[redacted]	[redacted]	[redacted]
Resource use	[redacted]	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; IPI, ipilimumab; NIVO, nivolumab; QALY, quality-adjusted life-year

Appendix K: Price details of treatments included in the submission

K1.1 Price of intervention

Table 121. Details of intervention costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source	Patient access scheme price
Nivolumab	Solution for infusion	40.0 mg	40.0 mg/4ml vial	£439.00	BNF[182]	[redacted]
		100.0 mg	100.0 mg/10ml vial	£1,097.00		[redacted]
		240.0 mg	240.0 mg/24ml vial	£2,633.00		[redacted]
Ipilimumab	Solution for infusion	50.0 mg	50.0 mg/10 ml vial	£3,750.00	BNF[182]	[redacted]
		200.0 mg	200 mg/40 ml vial	£15,000.00		[redacted]

K1.2 Price of comparators and subsequent treatments

Table 122. Details of comparators and subsequent treatment costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price	Source
Pembrolizumab	Solution for infusion	100.0 mg	1 vial	£2,630.00	BNF[182]
Fluorouracil	Solution for infusion	500 mg	1 vial	£3.43	eMIT 2023[180]
		1000 mg	1 vial	£3.04	eMIT 2023[180]
		2500 mg	1 vial	£4.12	eMIT 2023[180]
Leucovorin	Solution for injection	100 mg	1 vial	£4.56	eMIT 2023[180]
		300 mg	1 vial	£19.28	eMIT 2023[180]
		400 mg	1 vial	£126.25	BNF 2024[182]
Oxaliplatin	Solution for infusion	50 mg	1 vial	£6.47	eMIT 2023[180]
		200 mg	1 vial	£14.30	eMIT 2023[180]
Irinotecan	Solution for infusion	500 mg	1 vial	£43.38	eMIT 2023[180]
Capecitabine	Tablets	150mg	60	£8.10	eMIT 2023[180]
		300mg	60	£8.14	eMIT 2023[180]
		500mg	120	£22.51	eMIT 2023[180]
Cetuximab	Solution for infusion	100 mg	1 vial	£178.10	BNF 2024[182]
Panitumumab	Solution for infusion	100 mg	1 vial	£379.29	BNF 2024[182]
		400 mg	1 vial	£1,517.16	BNF 2024[182]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab plus ipilimumab for the treatment of adults and adolescents with untreated metastatic colorectal cancer with high microsatellite instability or deficient mismatch repair (ID1136)

Document B

Company evidence submission

Addendum to Sections B.3.8 – B.3.14 and Appendix J

August 2024

File name	Version	Contains confidential information	Date
		Yes	23rd August 2024

The following text is intended as an addendum to sections B.3.8 – B.3.14 of the Company evidence submission and Appendix J. Base case, sensitivity and scenario analyses of the adolescent population and the weighted population have been removed. Citations throughout this addendum refer to the references listed in Section B.4 of the original Company Submission.

B.3 Cost effectiveness

B.3.8 Base-case results

B.3.8.1 Base-case incremental cost-effectiveness analysis results

Base case analysis results are provided for the three populations of interest (adult, adolescent and weighted population). As can be seen, NIVO+IPI is considered to be a cost-effective use of NHS resources compared with comparator treatments across all populations of interest.

B.3.8.1.1 Adult population

The results of the base case analysis are summarised in Table 1 with disaggregated results in Appendix J. In terms of comparator treatments, the model predicts mean undiscounted LYs of [redacted] for PEMBRO and [redacted] for chemotherapy, correlating to discounted QALYs of [redacted] and [redacted], respectively. For chemotherapy, the majority of time was spent in progressed disease ([redacted] LYs in PD versus [redacted] LYs in PFS), while patients spent longer progression-free for PEMBRO ([redacted] PFS versus [redacted] PD).

By comparison, it was predicted that the use of NIVO + IPI will result in an additional [redacted] discounted QALYs versus PEMBRO and an additional [redacted] discounted QALYs versus chemotherapy (total: [redacted] discounted QALYs).

Total discounted costs associated with NIVO + IPI (with PAS), accrued over the modelled time horizon, were predicted to be [redacted], which was lower than PEMBRO (incremental: [redacted]) but had a higher cost versus chemotherapy (incremental: [redacted]). The resulting ICER estimates for NIVO + IPI were dominant versus PEMBRO, and £1,836 per QALY gained versus chemotherapy. Therefore, the base case ICERs are all substantially below a £30,000 per QALY willingness-to-pay threshold and NIVO + IPI can be considered a cost-effective use of NHS resources.

Table 1. Base-case results: adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,836

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 2. Base-case results: adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYG: life years gained; LYs: life years; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

B.3.9 Exploring uncertainty

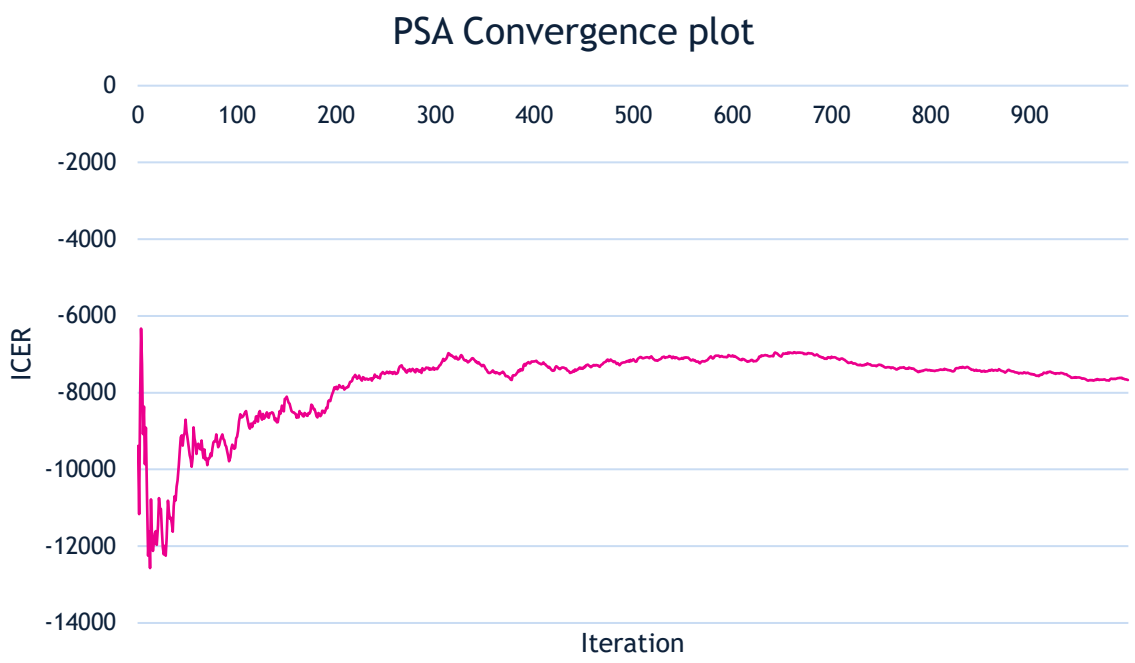
B.3.9.1 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the economic model samples values from distributions around the means of input parameters. Sampling utilises information of the mean and standard error of parameters to derive an estimated value using an appropriate distribution: costs, gamma; age and survival parameters, normal; utilities, probabilities and proportions, beta. These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters. The PSA is run separately for each comparator without applying a pre-set random number seed, leading to slight variations between runs even with identical model inputs.

Several inputs are derived from sources where it has not been possible to ascertain standard errors. To assess uncertainty surrounding these inputs, the standard error has been assumed to be 20% of the mean value for the purposes of the PSA.

As can be seen in Figure 1, convergence was reached after roughly 400 simulations. Therefore, running 500+ simulations gives a distribution of incremental results, and consequently, a robust estimate of the overall uncertainty surrounding cost-effectiveness results. Using the NMB approach, the probability of each treatment to be cost-effective at different levels of willingness-to-pay (WTP) per QALY is presented in the cost-effectiveness acceptability curve (CEAC).

Figure 1. PSA Convergence plot



Abbreviations: PSA, probabilistic sensitivity analysis

B.3.9.1.1 PSA results

PSA results are provided for the three populations of interest (adult, adolescent and weighted population), incorporating relevant NIVO + IPI PAS discounts. As can be seen, outcomes are comparable between the populations, underscoring the beneficial impact of NIVO + IPI across its licensed indication.

B.3.9.1.1.1 Adult population

Scatterplots for the base case analyses, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 2 (PEMBRO) and Figure 3 (chemotherapy), while cost-effectiveness acceptability curves (CEACs) are presented in Figure 4 (PEMBRO) and Figure 5 (chemotherapy). The PSA is run separately for each comparator without applying a pre-set random number seed, leading to slight variations between runs even with identical model inputs.

Based on these analyses, the probability that NIVO + IPI is cost-effective versus PEMBRO or chemotherapy is 100% and 100%, respectively, at a WTP threshold of £20,000/QALY gained and £30,000/QALY gained (Table 3).

Table 3. Probabilistic base-case results: adult population (with PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
Comparison of NIVO + IPI versus PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Comparison of NIVO + IPI versus chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£891

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 4. Probabilistic base-case results: adult population (no PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
Comparison of NIVO + IPI versus PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison of NIVO + IPI versus chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Figure 2. ICER scatterplot: NIVO + IPI versus pembrolizumab – adult population (with PAS)

Figure 3. ICER scatterplot: NIVO + IPI versus chemotherapy – adult population (with PAS)

Figure 4. Cost-effectiveness acceptability curve: NIVO + IPI versus pembrolizumab – adult population (with PAS)

Figure 5. Cost-effectiveness acceptability curve: NIVO + IPI versus chemotherapy – adult population (with PAS)

Figure 6. ICER scatterplot: NIVO + IPI versus pembrolizumab – adult population (no PAS)

Figure 7. ICER scatterplot: NIVO + IPI versus chemotherapy – adult population (no PAS)

Figure 8. Cost-effectiveness acceptability curve: NIVO + IPI versus pembrolizumab – adult population (no PAS)

Figure 9. Cost-effectiveness acceptability curve: NIVO + IPI versus chemotherapy – adult population (no PAS)

B.3.9.2 Deterministic sensitivity analysis

The deterministic sensitivity analysis (DSA) involves varying one parameter at a time and assessing the subsequent impact on the incremental costs, incremental QALYs and ICER. Each parameter is allocated a 'low' value and a 'high' value; unless otherwise stated, the low value is the lower bound of the 95% CI and the high value is the upper bound of the 95% CI (Table 5). By adjusting each parameter one at a time, the DSA assesses the impact of uncertainty around individual input parameters

on the model outcomes. Results are presented in tables and tornado plots, which clearly present the parameters that have the greatest effect on the relevant model outcomes. The most influential parameters are presented.

Table 5. Deterministic sensitivity analysis settings

Parameter		Unit	Base case value	Lower limit	Upper limit
Model settings	Cost discounting	%	3.5	0	6
	Effects discounting		3.5	0	6
Population settings	Age of population used	Years	60.9	48.72	73.08
	Percentage female	%	53.8	0	100
Mean time in progressed disease	Mean time in progressed disease state (PEMBRO and NIVO + IPI)	Months	1,271.07	772.82	1,769.32
Time on treatment	Chemotherapy - Mean time on subsequent treatment		20.16	13.05	28.80
	NIVO+IPI - Mean time on subsequent treatment		48.27	31.23	68.94
Resource use	Tumour marker test	Use per cycle	0.23	0.149	0.329
	Liver function test		1.15	0.744	1.643
	CT scan		0.3	0.194	0.429
	MRI scan		0.23	0.149	0.329
	Consultation outpatient appointment		2	1.294	2.86
	Best supportive care		0.92	0.595	1.31
Resource costs	Simple IV administration	£	286.71	190.79	421.11
	Complex IV administration		474.94	315.76	696.94
	Tumour marker test		15.3	9.90	21.85
	Liver function test		31.7	20.51	45.28
	CT scan		164.35	106.36	234.76
	MRI scan		249.61	161.53	356.54
	Consultation appointment		211.6	136.94	302.25
	Best supportive care		1,748.71	1,131.67	2,497.86
AE costs	Hepatitis	£	621.75	497.40	746.1
	Neutropenia		770.53	616.42	924.64
	Rash		5,63.06	450.45	675.67
	Diarrhoea/colitis		1,044.17	835.34	1,253.00
	Adrenal insufficiency		9,082.82	7,266.26	10,899.38
	Hyperthyroidism		1,791.55	1,433.24	2,149.86

	Hypophysitis		1,791.55	1,433.24	2,149.86
	Asthenia		3,285.97	2,628.78	3,943.16
	Decreased neutrophil count		770.53	616.42	924.64
	Hypertension		770.1	616.08	924.12
	Pneumonia		2,512.26	2,009.81	3,014.71
Utilities	Progression free utility	Utility	0.76	0.735	0.784
	Progressed disease utility		0.733	0.695	0.769

Abbreviations: AE, adverse event; CT, computed tomography; IPI, ipilimumab; IV, intravenous; MRI, magnetic resonance imaging; NIVO, nivolumab; PEMBRO, pembrolizumab

B.3.9.2.1 Deterministic sensitivity analysis results

Base case analysis results are provided for the three populations of interest (adult, adolescent and weighted population), incorporating relevant NIVO + IPI PAS discounts.

B.3.9.2.1.1 Adult population

Results of the deterministic sensitivity analysis are presented in Figure 10 (PEMBRO) and Figure 11 (chemotherapy) and demonstrate the impact of specific parameters on ICER estimates. In all scenarios, the ICER for NIVO + IPI versus comparators remained below the £30,000 per QALY willingness-to-pay threshold.

Plausible scenarios have been investigated further in Section B.3.9.3, in order to assess the impact of the uncertainty in the analysis.

Figure 10. DSA outcomes: NIVO + IPI versus pembrolizumab – adult population (with PAS)

Abbreviations: CT, computed tomography; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; IV, intravenous; MRI, magnetic resonance imaging; NIVO, nivolumab

Figure 11. DSA outcomes: NIVO + IPI versus chemotherapy – adult population (with PAS)

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

Figure 12. DSA outcomes: NIVO + IPI versus pembrolizumab – adult population (no PAS)

Abbreviations: CT, computed tomography; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

Figure 13. DSA outcomes: NIVO + IPI versus chemotherapy – adult population (no PAS)

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab

B.3.9.3 Scenario and one-way sensitivity analysis

As outlined in Sections B.3.8 (base case analysis results), B.3.9.1.1 (PSA results) and B.3.9.2.1 (DSA results), outcomes for the populations of interest remain relatively comparable. As a result, scenario and one-way sensitivity analyses have been undertaken using the adult population only, unless otherwise specified. Outcomes can be expected to be comparable for the adolescent and weighted populations.

B.3.9.3.1 Analysis of OS uncertainty

B.3.9.3.1.1 Alternative economic model time horizon

As previously discussed, there are limitations to the available evidence, particularly for OS data, within the economic model that have been addressed through plausible assumptions and scenario analysis. However, the initial five-year modelled period can be considered more robust, as it requires fewer assumptions and can be validated using observed trial data. Further, at this time point, first line treatment has already ceased and economic model clinical outputs can be validated against observed values from clinical trials, reducing uncertainty. This scenario analysis restricts the model time horizon to five years.

Results are provided in Table 6. As can be seen, total LYs and QALYs are decreased across all modelled treatment arms; however, NIVO + IPI maintains a benefit over PEMBRO and chemotherapy. First-line treatment costs remain unchanged by decreasing the time horizon, but resource use and subsequent treatment costs are lower than the base case analysis. This is particularly impactful versus chemotherapy, where incremental costs are slightly increased. However, ICERs remain below a £30,000/QALY willingness-to-pay threshold.

Table 6. Scenario analysis: five-year model time horizon - adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	£15,165

Costs and QALYs discounted; LYs undiscounted
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.9.3.1.2 Alternative source for PF-D transition

As outlined in Section B.3.3.2, there are limited data sources that can be used to estimate the PF-D transition. While general population mortality is applied in the base case analysis, CM142 PrePS data were available and have been applied as a scenario analysis.

There was a total of 164 patients used to inform this analysis (Cohort 2 [2L+ NIVO + IPI]: 119 patients; Cohort 3 [1L NIVO+IPI]: 45 patients), all of which received NIVO + IPI (Figure 14). The median time to death was not reached and the one-year survival probability was [redacted] (95% CI: [redacted]).

Figure 14. CM142 cohorts 2 and 3 pre-progression survival Kaplan-Meier data

As previously mentioned, there were few events so that the data can be considered extremely immature and should be viewed with caution, as evidenced by Figure 15.

As previously described for the TTP survival analysis, the best model fit was selected based on the model selection algorithm outlined in Palmer et al. (2023)[186] as well as via statistical tests such as AIC. The lognormal model is recommended based on low AIC value and plausible long-term extrapolation. For this scenario analysis, the economic model applies this data in addition to general population mortality.

Figure 15. CM142 cohort 2 (2L+ NIVO + IPI) and 3 (1L NIVO + IPI) PrePS standard parametric fits beyond trial period

Results are provided in Table 7. Total LYs and QALYs are decreased across all modelled treatment arms due to increased deaths from the progression-free state. This results in lower resource use for NIVO + IPI and PEMBRO; however, ICERs remain relatively unchanged.

Table 7. Scenario analysis: CM142 for PF-D transition - adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	£2,036

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.9.3.2 Analysis of uncertainty in long-term comparative effectiveness

B.3.9.3.2.1 Alternative ITC approaches to inform PEMBRO PF-PD transition

Three ITC approaches were undertaken to inform the comparison of NIVO + IPI and PEMBRO: fractional polynomial NMA; anchored or unanchored MAIC; and constant HR NMA. The fractional polynomial NMA was used in the base case analysis. Alternative approaches have been assessed in scenario analysis.

As shown in Table 8, across all ITC approaches, NIVO+IPI was predicted to be cost saving compared with PEMBRO. However, the unanchored MAIC and constant HR NMA predicted higher LYs and QALYs for PEMBRO while the anchored MAIC provided lower LYs and QALYs. Despite this, the ICER for NIVO+IPI remains dominant across all ITC approaches, demonstrating that NIVO+IPI offers a cost-effective use of NHS resources.

Table 8. Scenario analysis: alternative ITC approaches to inform PEMBRO PF-PD transition - adult population (with PAS)

	NIVO + IPI	PEMBRO			
		Base case	Anchored MAIC	Unanchored MAIC	Constant HR NMA
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	Dominant	Dominant	Dominant

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.9.3.2.2 Alternative TTP extrapolations for NIVO + IPI

Survival modelling using long-term extrapolation of parametric functions is subject to considerable uncertainty despite efforts to robustly and transparently provide survival curves that best represent patients in clinical practice. In order to assess the impact of alternative TTP parametric extrapolations on the cost-effectiveness of NIVO+IPI, survival curves described in the survival analysis report (Appendix O) have been applied within the model as scenario analyses.

This analysis should be viewed within the context of identifying the most appropriate survival extrapolation, as detailed in Section B.3.3.1. All extrapolations have been assessed for completeness. However, it should be noted that several of these extrapolations are not considered appropriate. Clinically implausible fits are presented in grey italics.

As shown in Table 9, across all extrapolations, NIVO+IPI is associated with improved QALYs compared with PEMBRO and chemotherapy and is cost-saving compared with PEMBRO across all TTP extrapolations, yielding dominant ICERs compared with PEMBRO. Although NIVO+IPI is generally associated with marginally higher

costs compared with chemotherapy, this is offset by improved QALYs so ICERs indicate that NIVO+IPI provides an acceptable use of NHS resources.

Table 9. Scenario analysis: alternative NIVO + IPI TTP extrapolations - adult population (with PAS)

NIVO + IPI TTP extrapolations (ordered by AIC)	PEMBRO			Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
Generalised Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,836
Lognormal	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,780
Log-logistic	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,754
Gompertz*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,779
Weibull	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,855
Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,887
Exponential*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£584

*Clinically implausible extrapolations, as outlined in Section B.3.3.1.1.1.
Abbreviations: AIC, Akaike information criterion; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TTP, time to progression

B.3.9.3.2.3 Alternative TTP extrapolations for chemotherapy

As outlined above for NIVO + IPI, chemotherapy TTP parametric extrapolations described in the survival analysis report (Appendix O) have been applied within the model as scenario analyses.

This analysis should be viewed within the context of identifying the most appropriate survival extrapolation, as detailed in Section B.3.3.1. All extrapolations have been assessed for completeness.

Across all extrapolations for alternative chemotherapy, NIVO+IPI is associated with higher costs than chemotherapy; however, improvements in QALYs result in ICERs that are substantially below a £30,000 per QALY willingness-to-pay threshold.

Table 10. Scenario analysis: alternative chemotherapy extrapolations - adult population (with PAS)

Chemotherapy TTP extrapolation (ordered by AIC)	NIVO + IPI versus Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
Lognormal	[redacted]	[redacted]	£1,736
Generalised Gamma	[redacted]	[redacted]	£1,836
Log-logistic	[redacted]	[redacted]	£1,764
Gamma	[redacted]	[redacted]	£1,746
Exponential	[redacted]	[redacted]	£1,735
Weibull	[redacted]	[redacted]	£1,743
Gompertz	[redacted]	[redacted]	£1,967

Abbreviations: AIC, Akaike information criterion; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TTP, time to progression

B.3.9.3.2.4 Comparison versus panitumumab + FOLFOX

Although direct trial evidence is not available for NIVO+IPI versus panitumumab, direct evidence is available for NIVO+IPI versus cetuximab-based therapy, which NICE has previously concluded has comparable efficacy to panitumumab-based therapy (TA709). Despite this conclusion, an ITC scenario analysis has been conducted to inform a comparison of NIVO+IPI versus panitumumab.

Table 11 reports model outcomes for a scenario using outputs from the ITC described in Section B.2.7.2.2.3. As can be seen, LYs and QALYs are broadly aligned with the overall chemotherapy arm from the base case analysis. However, costs are increased, so that NIVO + IPI has become cost saving. As a result, NIVO + IPI is dominant in this scenario.

Table 11. Scenario analysis: NIVO + IPI versus panitumumab + FOLFOX - adult population (with PAS)

	NIVO + IPI	Panitumumab + FOLFOX
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years

B.3.9.3.3 Analysis of uncertainty in subsequent treatment for chemotherapy arm

B.3.9.3.3.1 Alternative post-progression cost in chemotherapy arm

The base case analysis assumes that patients receiving chemotherapy in the first-line setting will receive NIVO + IPI in the second-line setting. However, some patients may not be eligible for second-line NIVO+IPI and may receive chemotherapy. This scenario aligns subsequent treatment in the chemotherapy arm with subsequent treatment in the NIVO + IPI and PEMBRO arms, applying equivalent costs.

Table 12 provides an overview of outcomes from this scenario analysis. As can be expected, LY and QALY outcomes remain consistent with the base case analysis. However, costs within the chemotherapy arm have decreased, resulting in an increased ICER (£16,785/QALY gained). However, this remains below a £30,000/QALY willingness to pay threshold, so that NIVO + IPI can still be considered a cost-effective use of NHS resources.

Table 12. Scenario analysis: alternative post-progression survival in chemotherapy arm - adult population (with PAS)

	NIVO + IPI	Chemotherapy
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	£16,785

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years

B.3.9.3.4 Analysis of uncertainty in utility values

B.3.9.3.4.1 Alternative health state utility values

The economic model uses treatment-specific progression free utility data, which is appropriate in the context of the statistically significant difference between the NIVO + IPI and chemotherapy arms during the utility analysis. However, a scenario analysis has assessed alternative health state utility values, as outlined in Table 13.

Table 13. Overall utilities from CM8HW compared with previous CRC HTAs

		Progression-free	Progressed
CM8HW	Overall	[redacted]	[redacted]
TA709 (KN-177)	PEMBRO	0.843	0.730
	Chemotherapy	0.787	0.730
TA439	Cetuximab, panitumumab and chemotherapy	0.767	0.64

Abbreviations: CRC, colorectal cancer; HTA, health technology assessment; PEMBRO, pembrolizumab

Table 14 provides an overview of outcomes. Using utilities from different sources has minimal effect on ICERs compared with the base case analysis; NIVO+IPI remains dominant compared with PEMBRO across all alternative utilities and has an ICER that represents a cost-effective use of NHS resources compared with chemotherapy.

Table 14. Scenario analysis: application of alternative utilities – adult population (with PAS)

	CM8HW overall utilities		TA709 utilities		TA439 utilities	
	PEMBRO	**Chemo**	**PEMBRO**	**Chemo**	**PEMBRO**	**Chemo**
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	Dominant	£2,151	Dominant	£1,715	Dominant	£2,074

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.9.3.5 Alternative cost and healthcare resource use

B.3.9.3.5.1 Alternative chemotherapy cost composition

The base case analysis applied chemotherapy costs that were weighted according to the proportion of patients receiving each regimen. This scenario analysis assessed the impact of alternative cost composition but assessing high-cost chemotherapy composition (100% panitumumab plus FOLFIRI; 100% cetuximab plus FOLFIRI) and a low-cost chemotherapy composition (100% FOLFOX).

Table 15 provides an overview of results. As expected, NIVO+IPI is cost saving compared with FOLFIRI + panitumumab and FOLFIRI + cetuximab with a dominant ICER. NIVO+IPI was associated with a higher cost than FOLFOX, but still yielded an ICER that suggests it is a cost-effective use of NHS resources.

Table 15. Scenario analysis: alternative chemotherapy costs – adult population (with PAS)

Chemotherapy composition	NIVO + IPI versus Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER versus NIVO + IPI (£/ QALY)
Panitumumab plus FOLFIRI	[redacted]	[redacted]	Dominant
Cetuximab plus FOLFIRI	[redacted]	[redacted]	Dominant
FOLFOX	[redacted]	[redacted]	£2,361

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab

B.3.10 Subgroup analysis

B.3.10.1 Analysis of centrally confirmed dMMR/MSI-H CheckMate 8HW subgroup

The base case analysis applies evidence from the CM8HW ITT population. However, the CM8HW included a subgroup of patients with centrally confirmed dMMR/MSI-H status. This scenario analysis reflects this subgroup of patients.

Table 16 provides an overview of results. LYs and QALYs are increased across all treatment arms so that incremental QALYs for NIVO + IPI versus comparators remained comparable with the base case analysis. However, this has a consequent increase in resource use and subsequent treatment costs that improve cost savings for NIVO + IPI versus comparators. As a result, NIVO + IPI is dominant versus both PEMBRO and chemotherapy.

Table 16. Subgroup analysis: centrally confirmed dMMR/MSI-H CM8HW – adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	Dominant

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B.3.11 Summary of sensitivity analysis results

A large number of sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model. In the deterministic analysis, NIVO + IPI was cost-effective against all scenarios at a WTP threshold of £30,000/QALY. Similarly, in the PSA, the probability that NIVO + IPI is cost-effective versus PEMBRO is 100% and versus chemotherapy is 100% at a WTP threshold of £20,000/QALY gained and £30,000/QALY gained.

Plausible alternative inputs and assumptions were assessed as scenario analyses within Section B.3.9.3, as depicted in Figure 16. Reflecting the PSA and deterministic sensitivity analysis, all of the ICERs remain below the £30,000/QALY threshold.

Figure 16. Scenario analysis: overview of all scenarios

Abbreviations: PEMBRO, pembrolizumab; QALY, quality-adjusted life-years

B.3.12 Benefits not captured in the QALY calculation

As stated by the Bowel Cancer UK during engagement for TA709, dMMR/MSI-H is a rare subtype of CRC with limited treatment options available. Although PEMBRO has been recommended in patients who were previously untreated, NIVO + IPI provides an efficacious alternative to PEMBRO with a different mechanism of action, thus increasing therapeutic diversity. Additionally, NIVO + PEMBRO would be the first immune-oncology therapy for adolescent patients with dMMR/MSI-H mCRC to be assessed by NICE.

NIVO + IPI is a highly innovative, targeted immuno-oncology therapy with a unique mechanism of action and published data describing the beneficial impact of therapy in terms of efficacy and safety. The synergistic mechanism of action, targeting multiple receptors at once, has the potential to increase response and may be preferable to treatment that only targets one receptor.

Further, in the context of the clinical benefits observed in CM142 and CM8HW, the use of NIVO + IPI may result in potential substantial HRQoL benefits for patients' caregivers that are not reflected in the QALY calculation.

For dMMR/MSI-H mCRC, there are additional challenges to adequately capturing benefits. There are fewer patients to inform collection of robust, nuanced HRQoL data compared with the overall mCRC population. Additional, historical alternatives have poorer efficacy so that a robust, nuanced QALY calculation is challenging, both practically and ethically.

B.3.13 Validation

A technical review of the cost-effectiveness model was conducted by an independent economist. Further, the relevance of the model structure and assumptions were validated through consultation with UK clinicians. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

In general, where no evidence has been identified, simple assumptions have been made based on independent sources, such as published literature, CRC guidelines or previous NICE appraisals in the field of CRC. These assumptions were then assessed for clinical plausibility; uncertainty has been characterised through the use of sensitivity analyses. Extensive sensitivity analyses were then undertaken, and all ICERs remain below a £30,000/QALY threshold.

B.3.13.1 Validation of cost-effectiveness analysis

B.3.13.1.1 Validation to observed KEYNOTE-177 outcomes

Long-term survival outcomes are available from KN-177 and can be used to assess the clinical plausibility of economic model outcomes.

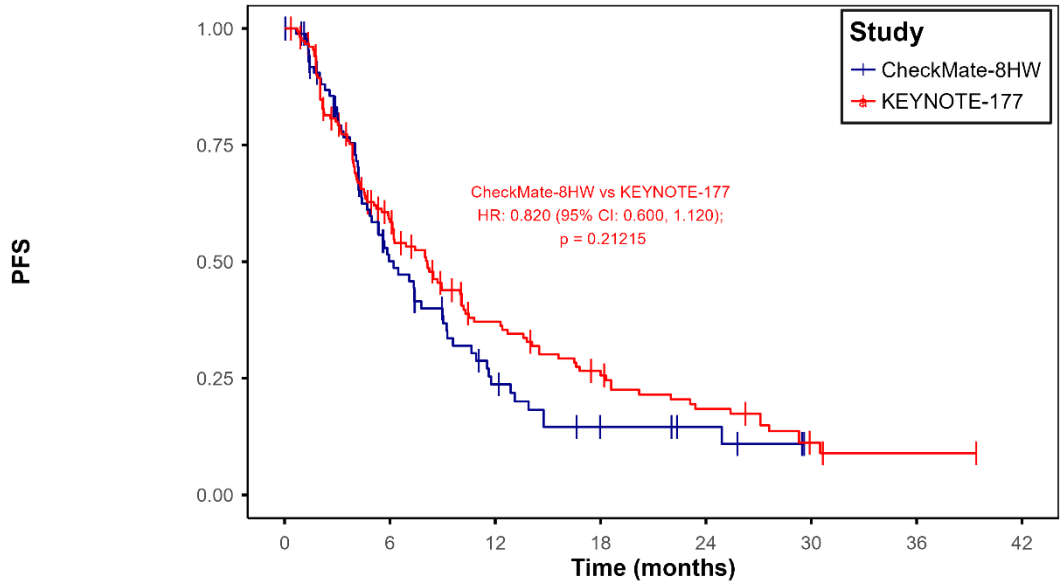
B.3.13.1.1.1.1 Chemotherapy arm

Table 17 demonstrates that OS outcomes for chemotherapy are initially higher in the economic model than in KN-177. However, by year five, OS is lower in the economic model than in KN-177.

This can be expected, as chemotherapy PFS outcomes for CheckMate 8HW are numerically lower than for KEYNOTE-177, although not statistically significant (Figure 17). The reasons for this are not entirely clear, as outcomes are aligned by 24 months. One possible rationale is slightly higher bevacizumab usage in KN-177, although this has limited impact on the comparison of NIVO + IPI versus chemotherapy, as shown in Table 31 of the original Company Submission. Additionally, this difference may be a result of crossover to NIVO + IPI in CM8HW. However, results for PFS per BICR using the EMA definition, which does not apply censoring at subsequent anti-cancer therapy initiation, were consistent with the primary analysis ([redacted]).[114] As such, neither rationale would impact on the understanding of NIVO + IPI versus chemotherapy.

As the economic model applies CM8HW TTP to inform the PF-PD transition for the chemotherapy arm, it can be expected that increased progression will increase movement to the progressed disease state and hence OS. Further, pre-progression LYs for the chemotherapy arm are broadly aligned with output from the TA709 economic model, as outlined in Table 19. Overall mean LYs are higher than the TA709 economic model, due to inclusion of NIVO + IPI as a second-line treatment.

Figure 17. Comparison of chemotherapy PFS for CM8HW and KN-177



NAR (Cumulative Events)

CheckMate-8HW	101 (0)	35 (39)	14 (56)	6 (61)	4 (61)	0 (62)	0 (62)	0 (62)
KEYNOTE-177	154 (0)	81 (60)	43 (88)	27 (101)	18 (108)	5 (114)	3 (115)	0 (115)

Abbreviations: PFS, progression-free survival

B.3.13.1.1.1.2 Pembrolizumab arm

Survival outcomes for pembrolizumab are broadly aligned between KN-177 and the economic model, although slightly lower by year 5. However, all values are within a plausible range.

Table 17. Comparison of economic model outcomes and KN-177

		1 year OS, %	3-year OS, %	5-year OS, %
Chemotherapy	Base case	[redacted]	[redacted]	[redacted]
	KN-177[187,200]	74.0	50.3	44.2
Pembrolizumab	Base case (fractional polynomial)	[redacted]	[redacted]	[redacted]
	Anchored MAIC	[redacted]	[redacted]	[redacted]
	Unanchored MAIC	[redacted]	[redacted]	[redacted]
	Constant HR	[redacted]	[redacted]	[redacted]
	KN-177[187,200]	77.8	61.4	54.8

Abbreviations: HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival

B.3.13.1.2 Validation of NIVO + IPI outcomes versus CheckMate 142 Cohort 3 (1L NIVO + IPI) and Cohort 2 (2L+ NIVO + IPI)

NIVO + IPI survival outcomes are available from CM142 Cohort 3 (1L NIVO + IPI) and Cohort 2 (2L+ NIVO + IPI). As a result, these can be used to assess the clinical plausibility of economic model outcomes. Table 18 shows that the economic model initially predicts OS higher than that observed in clinical trial. However, by year two, survival outcomes from the economic model are broadly aligned with CM142 cohort 3 (1L NIVO + IPI) and Cohort 2 (2L+ NIVO + IPI).

Table 18. Comparison of economic model outcomes and CM142 cohort 3 (1L NIVO + IPI)

	Economic model	CM142 cohort 3 (1L NIVO + IPI)	CM142 cohort 2 (2L+ NIVO + IPI
1-year OS, %	[redacted]	84.1	84.9
2-year OS, %	[redacted]	79.4	74.8
5-year OS, %	[redacted]	67	67.9

Abbreviations: OS, overall survival

B.3.13.1.3 Validation to TA709 outcomes

TA709 reports survival outcomes for PEMBRO and key comparators.[1] Table 19 provides a comparison of survival outcomes from TA709 versus the economic model. As can be seen, predicted pre-progression LYs are broadly comparable with values output from TA709. However, progressed disease LYs are impacted by the use of immunotherapies as a subsequent treatment, particularly for chemotherapy.

Table 19. Comparison of survival outcomes between TA709[125] and current economic model

Comparator	Appraisal	Total LYs	Progression-free LYs	Progressed disease LYs
Pembrolizumab	TA709	6.93	4.56	2.37
	Current	[redacted]	[redacted]	[redacted]
SoC/CAPOX	TA709	3.78	1.21	2.57
	Current	[redacted]	[redacted]	[redacted]
Panitumumab+ FOLFOX	TA709	4.10	1.55	2.55
	Current	[redacted]	[redacted]	[redacted]

Abbreviations: CAPOX: capecitabine, oxaliplatin; FOLFOX: fluorouracil, folinic acid, oxaliplatin; LY: life year; SOC: standard of care.

B.3.14 Interpretation and conclusions of economic evidence

Base case analysis

- Use of NIVO + IPI results in incremental QALYs of [redacted] versus PEMBRO and [redacted] versus chemotherapy.
- After accounting for a PAS, discounted incremental costs were estimated to be [redacted] versus chemotherapy and cost saving versus pembrolizumab ([redacted]).
- The resultant ICER was £1,836 per QALY versus chemotherapy, which is considered to be cost-effective at a willingness-to-pay threshold of £30,000 per QALY.
- NIVO + IPI was considered to be dominant versus PEMBRO.

Sensitivity analysis

- In the probabilistic sensitivity analysis and deterministic sensitivity analysis, NIVO + IPI was cost-effective in all scenarios at a willingness-to-pay threshold of £30,000 per QALY.
- Extensive scenario analyses and one-way sensitivity analyses were undertaken, reflecting the assumptions required to undertake plausible, robust and transparent base case analysis. Within these scenario analyses, all of the ICERs remain below the £30,000 per QALY threshold.
- Therefore, NIVO + IPI can be considered a cost-effective use of NHS resources.

The population included in the economic evaluation was consistent with the UK population eligible for NIVO + IPI as per the anticipated licence. Clinical efficacy was derived from CM8HW, which reflects the adult patient population of interest in the UK.

The analysis is directly applicable to clinical practice in England:

- As outlined in B.2.10.3 of the original submission, the patient population of CM8HW is reflective of UK patients with dMMR/MSI-H mCRC.
- The comparators available within the model reflect UK clinical practice and the NICE final scope.[184]
- The resource utilisation and unit costs are reflective of UK clinical practice and were derived from the National schedule of NHS costs and aligned with previous NICE mCRC HTA preferences.
- A pharmacokinetic simulation study concluded that the exposure of the proposed dosing regimen for both NIVO and IPI in adolescents is expected to result in comparable benefits and risks to those in adults.

Further, the analysis performed makes use of the best available evidence to inform the model. Although there are several areas of uncertainty, extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs. Direct head-to-head data were not available for NIVO + IPI versus PEMBRO; however, several ITC methodologies have been employed to explore the uncertainty around indirect estimates of comparative effectiveness, all of which have been applied in the economic model.

A number of patients in the chemotherapy arm crossed over to receive NIVO + IPI as a subsequent treatment. However, these patients did not impact on the economic model as an independent source of efficacy was applied to inform PPS. Further, no crossover analysis has been undertaken, as results for PFS per BICR using the EMA

definition, which does not apply censoring at subsequent anti-cancer therapy initiation, were consistent with the primary analysis ([redacted]).[114]

In summary, availability of NIVO + IPI would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need. The adoption of NIVO + IPI in this therapeutic indication in NHS England would represent a further, significant advance in the management of this life-threatening condition and would be a cost-effective use of NHS resources.

Appendix J: Clinical outcomes and disaggregated results from the model

J1.1 Clinical outcomes from the model

Clinical outcomes are summarised in Table 20 (adult population). Comparison with outcomes in clinical trials are provided in Section B.3.13.1.

J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Clinical outcomes are summarised in Table 20 (adult population).

Table 20. Base case analysis results: disaggregated outcomes for adult population (with PAS)

	NIVO + IPI	Pembrolizumab	Chemotherapy
Clinical outcomes			
QALYs (discounted)	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Disutility of grade 3-4 AE	[redacted]	[redacted]	[redacted]
Life years (undiscounted)	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]
Cost outcomes (discounted)			
Total Costs	[redacted]	[redacted]	[redacted]
Treatment-related costs	[redacted]	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]	[redacted]
Total resource use	[redacted]	[redacted]	[redacted]
Resource use	[redacted]	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; IPI, ipilimumab; NIVO, nivolumab; QALY, quality-adjusted life-year

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's a plain English summary of their submission written for patients participating in the evaluation. It's 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's 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

Both generic and brand name.

Nivolumab + ipilimumab (Opdivo® + Yervoy®)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Nivolumab + ipilimumab will be used in people aged 12 years and older with previously untreated colorectal cancer (CRC) with high microsatellite instability or mismatched repair deficiency whose tumour has metastasised or where surgical resection is not an option. CRC is a malignant tumour that arises from the lining of the large intestines (colon and rectum). CRC is generally considered advanced when the primary cancer has spread to another part of the body (metastatic) or in some cases has spread into tissues around the bowel or nearby lymph nodes (locally advanced).[1] Metastatic CRC (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes.[2] The most common sites of metastasis are the liver, the lungs and the peritoneum (muscular layer which lines the abdomen); however, the cancer may also spread to other sites, such as the bones or the brain.[3] In normal cells, a mechanism called mismatch repair (MMR) ensures that structural changes to DNA are corrected, limiting damage and preventing cancer development. For every 100 people with mCRC tumours in the UK, 4 or 5 these people are classified as mismatch repair deficient (dMMR), meaning that their cells lack the machinery required to repair this DNA damage.[4,5] This results in tumours

with more frequent changes (mutations) in repetitive DNA sequences known as ‘microsatellites’, leading to ‘microsatellite instability’.[6-8]

Tumours with dMMR or high microsatellite instability (MSI-H) are biologically distinct from tumours that are microsatellite stable or have low microsatellite instability. Further, the dMMR/MSI-H subtype is associated with poorer prognosis compared with other metastatic tumours.[2,9-12]

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.

Scientific Advice with the MHRA for this indication currently underway (meeting July 2024), with a view to proposing a national route submission in September 2024. The estimated timelines are as follows:

Estimated Regulatory Timelines

GB submission: September 2024

[redacted]

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:

BMS has contracted and paid GUTS UK and Heartburn Cancer UK for advice on production of patient materials for oesophago-gastric cancer.

BMS have two ongoing collaborations with Macmillan Cancer Support regarding forecasting and rehabilitation in cancer.

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.

CRC is the third most common cancer diagnosed worldwide,[13] and the fourth most common cancer in the UK.[14] In 2020, 34,405 new cases of CRC were diagnosed in England, and of these, 16,835 (48.9%) were diagnosed at stage III or IV, at which stage the cancer has spread beyond the muscle layer of the bowel.[14]

The number of cases of CRC increases with age, and is highest in people aged 70-79 years, with more than 9 in 10 cases diagnosed in people aged 50 years and older.[14] However, the incidence of CRC in the population aged under 50 is increasing,[15] with those under 50 more likely to be diagnosed with more severe disease.[16] Around 55 in 100 cases of CRC are diagnosed in men.

Survival is highly dependent on the stage of the CRC at diagnosis. If it is diagnosed at an early stage, 5-year survival can be higher than 90%. However, if the cancer has already spread to distant sites, only 10% of patients can be expected to survive up to 5 years.[17] There were 14,033 deaths due to CRC in 2020.[14]

Symptoms of CRC include changes in bowel habits that do not go away over time, (such as needing the toilet more frequently, looser stools, pain in the stomach); blood in the stools not caused by haemorrhoids; pain in the stomach; discomfort or bloating after eating; a noticeable lump in the stomach; a feeling of needing to strain when defecating; weight loss; and anaemia, resulting in tiredness.[18,19] These symptoms can occur in isolation or combination.[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?

Patients might suspect CRC based on symptoms, which include bleeding from the rectum, abdominal bleeding, diarrhoea/constipation, weight loss, tiredness and breathlessness. CRC might also be suspected based on physical examination or the results of blood/faecal tests.[20] CRC is confirmed by viewing a small piece of removed tissue under a microscope;[20] disease stage and metastatic status are identified by medical imaging.

Current guidelines in the UK recommend that all people with CRC should have a sample of their tumour tested for dMMR/MSI-H.

Since eligibility for certain treatments is influenced by an individual's genetics, testing for other mutations (i.e., RAS or BRAF V600E) is also performed in all people with mCRC who are suitable for systemic treatment, at diagnosis of metastatic disease.[21]

There are no new diagnostic tests required with this new treatment.

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.

The choice of therapy for CRC depends on a number of factors including genetic subtype; disease severity; location of the tumour in the bowel; whether the individual has other medical conditions; and extent of previous treatment.

In untreated dMMR/MSI-H mCRC, pembrolizumab is currently the only treatment specifically recommended by NICE for the treatment of adult patients.[22]

In some cases, where patients have very advanced disease and for whom pembrolizumab is not suitable, patients are treated with chemotherapy (most commonly FOLFOX, FOLFIRI or CAPOX). Depending on the type of tumour, and where the tumour is, some patients are offered more intense chemotherapy called FOLFOXIRI, or might have cetuximab or panitumumab added to their FOLFOX or FOLFIRI chemotherapy.

It is anticipated that nivolumab in combination with ipilimumab will be used for the treatment of adults and adolescents with previously-untreated unresectable or metastatic CRC with dMMR/MSI-H. At the moment, most of these patients are treated with pembrolizumab.

Patients whose disease progresses whilst receiving nivolumab + ipilimumab or pembrolizumab, and are still fit for treatment, would be treated with chemotherapy. Those receiving chemotherapy as their first treatment can receive nivolumab + ipilimumab or pembrolizumab if their disease progresses and are suitable for treatment.

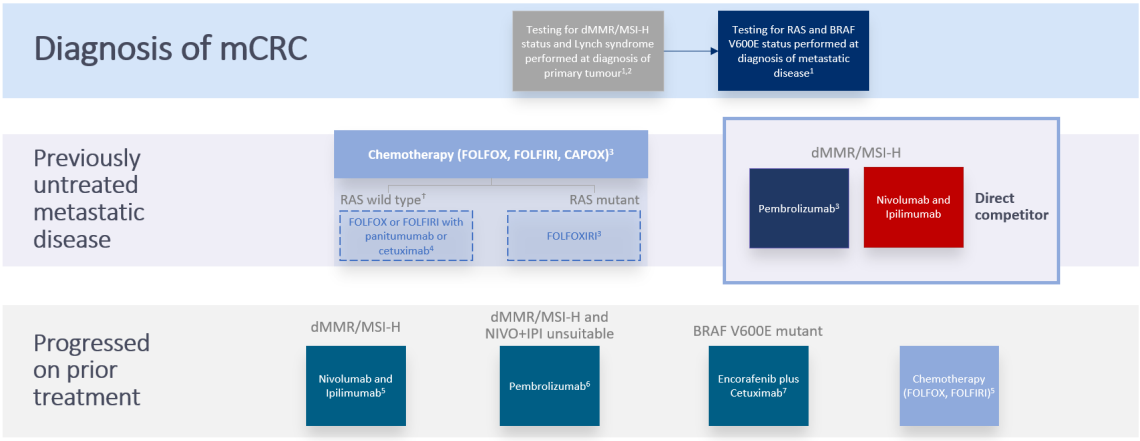


Figure 1. Systemic treatment options for mCRC and the positioning of nivolumab + ipilimumab in the treatment pathway[21-28]

Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficiency; EGFR, epidermal growth factor receptor; MSI-H, microsatellite instability high

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 mCRC may experience severe symptoms. The cancer and its treatment may cause physical changes in the body, which can be very distressing and may affect the way patients feel about themselves. Some patients may have received previous surgery for their cancer, such as a colostomy or ileostomy, which are difficult to cope with and may have caused scarring; additionally, living with a stoma can be extremely distressing for patients. Other symptoms, such as persistent diarrhoea or constipation, impact greatly upon patients' everyday lives. Toileting difficulties are often difficult to talk about, so patients may feel reluctant to share the burden with loved ones.[29]

There are very few patients with the type of mCRC that is specific to this submission, i.e., dMMR. Hence, there is little publicly available patient-based evidence available for this group.

Evidence suggests that once at the metastatic stage, outcomes are poorer in patients with dMMR than in patients without,[4] so if any comparisons can be drawn, it is to suggest that outcomes may be poorer rather than better in this group.

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.

The immune system consists of complex processes used by the body to fight illnesses. When the immune system detects something harmful, it makes antibodies that attaching to the foreign cells, so that they can be recognised as harmful and are destroyed by white blood cells.

To stop the immune system from attacking healthy cells, the body uses immune checkpoints. Cancer cells find ways to hide from the immune system by activating these checkpoints. The aim of immunotherapy cancer treatments called *checkpoint inhibitors* is to stop cancer cells from activating these checkpoints, which will then allow the immune system to help destroy the cancer cells.[30,31]

Nivolumab and ipilimumab are examples of checkpoint inhibitors. They each target different checkpoints. Nivolumab blocks the activity of a checkpoint called PD-1, a protein that prevents the white blood cells from recognising and attacking cancer cells. Ipilimumab blocks the activity of a protein called CTLA-4, which prevents white blood cells from attacking normal body cells and cancer cells. This double action increases white blood cell activity, which allows the immune system to recognise, attack and destroy the cancer cells.[32]

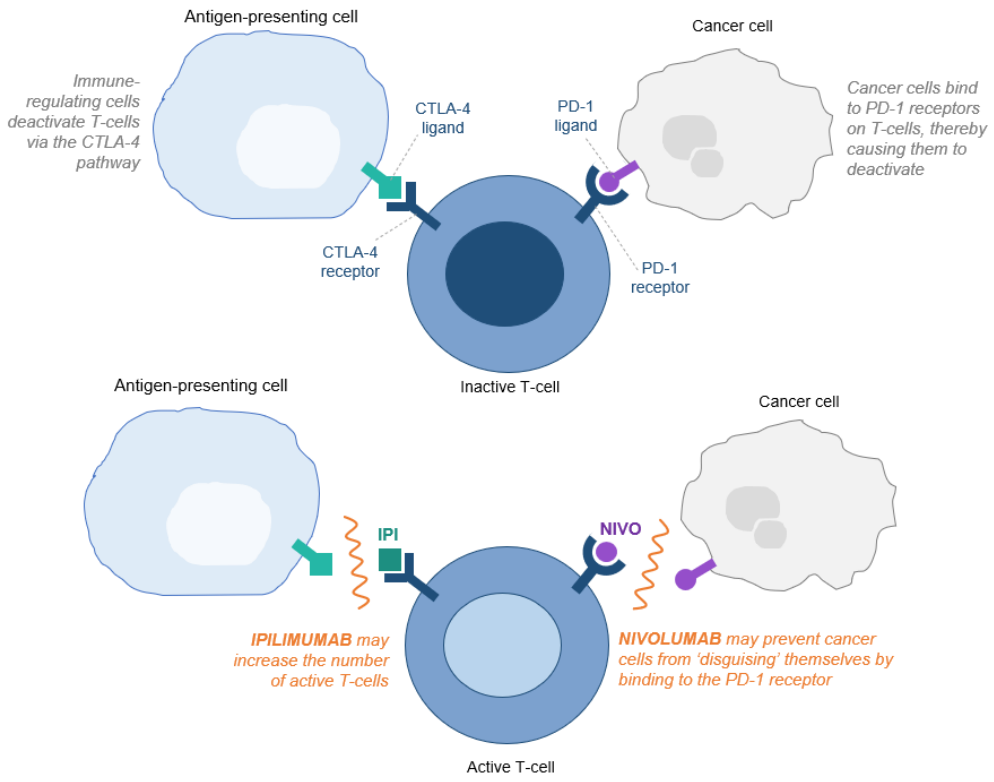


***Figure 2**. Mechanism of action for nivolumab and ipilimumab*

A video of how checkpoint inhibitors work is available on the Cancer Research UK website; https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy/types/checkpoint-inhibitors

Studies have shown that the tumour-type within this submission (dMMR/MSI-H) are particularly sensitive to immune checkpoint blockade therapy.[5,33] Patients with CRC that have this type of tumour are expected to respond well to immunotherapy.[34]

Due to this innovative mechanism of action and the nature of the immune system, treatment with immunotherapy results in long-term improvements to delaying disease progression, even after people have stopped treatment.

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.

Nivolumab + ipilimumab are administered in combination for adolescent and adult patients with dMMR or MSI-H mCRC and are not intended to be used in combination with other medicines. Sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) include data for nivolumab + ipilimumab delivered in combination.

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?

Nivolumab + ipilimumab is administered in a similar way to chemotherapy. It is given by an intravenous (IV) infusion. Infusions are often given in a hospital outpatient infusion clinic, but some treatment centres offer infusions in other settings, which can be closer to your home.

In adults and adolescent patients aged 12 years and older who weigh more than 40 kg, nivolumab (240 mg) is administered in combination with ipilimumab (1 mg/kg) as separate 30-minute infusions once every three weeks for four doses. After this point, nivolumab (240 mg) is administered alone as a 30-minute intravenous infusion every two weeks, or nivolumab (480 mg) is administered alone as a 30-minute intravenous infusion every four weeks.

In adolescent patients aged 12 years and older who weigh less than 40 kg, nivolumab (3 mg/kg) is administered in combination with ipilimumab (1 mg/kg) as separate 30-minute infusions every three weeks for four doses. After this point, nivolumab (3 mg/kg) is administered intravenously every two weeks.

Treatment would be initiated and supervised by a doctor who is experienced in the treatment of cancer. The treatment should be continued as long as there is clinical benefit, up to two years in total, but should be stopped if the patient is not reacting well to it

.

Although treatment with nivolumab + ipilimumab is longer than treatment with chemotherapy, the intensity of this treatment decreases after 3 months, at which stage only a monthly 30-minute infusion is required.

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.

CheckMate 8HW (NCT04008030) is a global study of nivolumab monotherapy, nivolumab plus ipilimumab, or investigator's choice chemotherapy for the treatment of participants with dMMR/MSI-H mCRC. The study remains ongoing. Updated analyses will include exploring progression-free survival (PFS; the length of time during which the disease does not progress and patients do not die) for nivolumab + ipilimumab compared with nivolumab monotherapy. If certain statistical criteria are met, other analyses of overall survival (OS; how long patients live) and overall response rate (the proportion of patients who achieve tumour shrinkage in response to treatment) will be performed in patients receiving different treatments

at different stages in the treatment pathway, including nivolumab + ipilimumab vs. chemotherapy.

There were 303 participants in CheckMate 8HW who had not received any prior treatment. To take part, people had to:

- be 18 years or older
- have confirmed diagnosis of recurrent or metastatic CRC with known MSI-H or dMMR status.
- have an adequate level of physical functioning and be able to perform work of a light nature.

People could not take part in the CheckMate 8HW trial if they have:

- an autoimmune disease
- a history of interstitial lung disease or pneumonitis
- a history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

CheckMate 142 is a completed clinical trial that studied nivolumab administered either by itself or in combination with ipilimumab in 45 people who have recurrent and metastatic MSI-H and non-MSI-H colon cancer. In this trial, the effect of treatment with nivolumab or nivolumab + ipilimumab on tumour size, disease progression and patient survival was studied. In this analysis, nivolumab + ipilimumab demonstrated improvements in response rates and long-term survival.

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.

Nivolumab + ipilimumab provides an alternative to pembrolizumab or chemotherapy in people with previously untreated dMMR/MSI-H mCRC. The main clinical trial (CheckMate 8HW) compared how well patients responded to nivolumab + ipilimumab compared with patients who were given chemotherapy.

At 5.9 months since starting treatment, half of the patients receiving chemotherapy either experienced disease progression or death, compared with less than 20% of patients receiving nivolumab + ipilimumab experiencing worsening of their disease or death at this point. This benefit was sustained, and at 24 months, 72% of

patients had not experienced disease progression or death.[35,36] More details can be found in Section B.2.4.6.2 of the Company Submission.

In another clinical trial, CheckMate 142, 71% of patients with dMMR/MSI-H CRC who had been treated with prior therapy, and received with nivolumab + ipilimumab in the trial, displayed a complete or partial response to treatment, meaning that their tumour was either removed or significantly reduced in size.

As outlined previously, OS describes the total length of time that patients survive after starting their treatment. For statistical analysis to be conducted, half of the patients who received nivolumab + ipilimumab would need to have died; however, this had not occurred after 32 months of analysis. In CheckMate 142, after 60 months (5 years) of follow-up, 67% of patients who received nivolumab + ipilimumab were still alive.

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.

mCRC places a significant burden on patients and significantly impacts their quality of life. The symptoms, including fatigue, anaemia, bowel changes, abdominal pain and breathlessness, can impact all aspects of a patient's life.[37,38]

CheckMate 8HW included an assessment of patient's health-related quality of life during the trial using an EQ-5D-3L questionnaire, which captures mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression. This data will be analysed and published in the future.

Across the population, patients whose disease had not progressed reported better health-related quality of life than people whose disease had worsened. In addition, people who had been treated with nivolumab + ipilimumab reported better health-related quality of life than patients who received chemotherapy, which was sustained over the trial period.

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.

Nivolumab and ipilimumab have been studied extensively in patients with different types of cancer as part of clinical trials. Both are generally well tolerated, but like any medication, each can cause side effects. As both nivolumab and ipilimumab target the immune system, certain side effects are caused when the immune system becomes over-active and begins to attack healthy cells. These side effects are different from the ones typically seen with chemotherapy, which works by killing fast-growing cells, such as cancer cells.

The potential harms of the nivolumab + ipilimumab regimen for the treatment of mCRC were investigated in the CheckMate 8HW phase 3 trial. The most frequent treatment-related side effects were itching (occurring in 22.5% of patients), diarrhoea (21.0%), hypothyroidism (16.0%) and physical weakness/lack of energy (14.0%).[36,39,40] In the clinical trial, 17% of patients who received nivolumab + ipilimumab needed to discontinue treatment because of treatment related side effects, compared with 32% of patients on chemotherapy.[40,41]

Immune-related side effects are usually medically manageable by withholding or withdrawing the drug or using steroids or other medications that suppress the immune system. As nivolumab + ipilimumab is already used to treat other types of cancer in England, such as advanced melanoma and renal cell carcinoma, clinicians are familiar with the monitoring and management needs of common side effects related to immunotherapy. Management algorithms and hospital procedures are available and well-developed, and patients are fully informed on how to monitor themselves for potential side effects following treatment with nivolumab + ipilimumab. NHS Oncology treatment centres run 24-hour oncology helplines are so that patients can report side effects any time.

Based on available evidence, the safety profile of nivolumab + ipilimumab can be considered manageable and acceptable in the context of alternative therapies, such as standard chemotherapy regimens. No new safety concerns were identified for nivolumab + ipilimumab in CheckMate 8HW. Overall, adverse events were consistent with immunotherapy and the established safety profile of this treatment in other tumour types.

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

More treatment options for people with mCRC are needed. This is particularly true for patients with the dMMR/MSI-H subtype, as there is reason to believe that these patients may do worse than those without this subtype.[4]

Nivolumab + ipilimumab is already routinely used in people with dMMR/MSI-H mCRC who have already received a course of chemotherapy. As such, there is already evidence demonstrating that nivolumab + ipilimumab is effective and that patients with CRC respond well to immunotherapy treatments.[5,33] The aim of this submission is to expand the use of a demonstrated safe and effective treatment to other people with mCRC who have very limited specific treatment options.

The CheckMate 8HW trial is demonstrating a meaningful improvement in PFS for people with dMMR/MSI-H mCRC who have received treatment with nivolumab + ipilimumab, compared with patients who have received chemotherapy. After 12 months, 79% of patients who received nivolumab + ipilimumab had not experienced disease progression or death, compared with only 21% of the people who received chemotherapy.[36,39] Results from CheckMate 8HW further demonstrated that people benefit from treatment with nivolumab + ipilimumab irrespective of their age, tumour type/location, or where their tumour had spread.

In CheckMate 142, 70% of people had an overall response to treatment with nivolumab + ipilimumab, and 67% were still alive after 60 months (5 years).[42]

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

Due to the way that nivolumab + ipilimumab attacks cancer cells, patients are at increased risk of developing immune-related side effects of treatment than if they were treated with chemotherapy. In some cases, this might lead to people needing to discontinue their treatment as a result of these side effects. In the CheckMate 8HW clinical trial, the most frequently occurring severe immune-related side effects in people who received nivolumab + ipilimumab were diarrhoea/colitis (5%), adrenal insufficiency (inadequate production of hormones by the adrenal glands; 4%) and hepatitis (3%).[36,40] Of these, most events were manageable using established treatment guidelines or by administering corticosteroids.

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.

An economic model has been developed to assess the value of nivolumab + ipilimumab to the NHS. The model uses the results of the CheckMate 8HW and CheckMate 142 clinical trials. The model can estimate the long-term benefits of treatment and inform whether these therapies offer value for the healthcare system.

Within the model, people are assigned to one of three groups (health states):

- Progression-free disease – people whose disease has not gotten worse since they began treatment
- Progressed disease – people whose disease has gotten worse since they began treatment
- Death – people who have died since starting treatment, either due to their disease or from another cause

The movement between these health states (indicated by the arrows below), reflects a patient's real-world experience as their cancer progresses (or is delayed from progressing as a result of effective treatment). Movement between health states is modelled using probabilities that are calculated primarily from outcomes (PFS and OS) from the CheckMate 8HW and CheckMate 142 clinical trials.

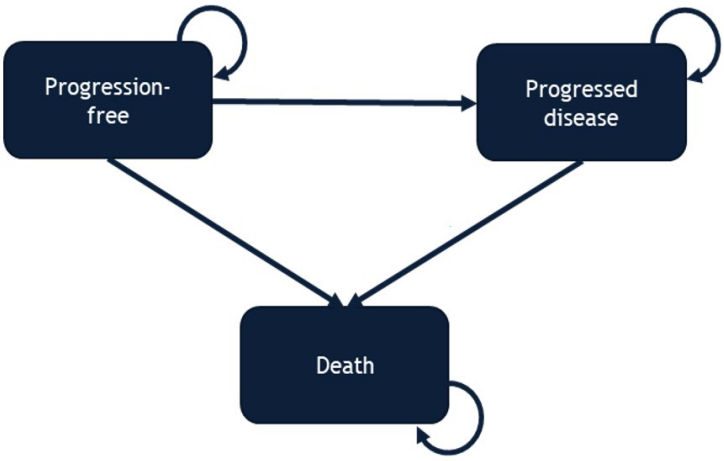


Figure 3. Overview of model schematic used to assess the cost-effectiveness of nivolumab + ipilimumab for adult and adolescent patients with dMMR/MSI-H mCRC

As clinical trials monitor patients over a short period of time, but the effect of cancer and the potential benefits of treatment can affect patients for much longer periods, the economic model makes long-term predictions based on survival outcomes observed in the trial. The need to extrapolate beyond the observation period of a clinical trial is common in appraisals of cancer therapies, and allows the long-term effects of treatment with nivolumab + ipilimumab to be predicted over the remainder of a patient's life.

In addition, the impact that treatment with nivolumab + ipilimumab has on patients' quality of life, in combination with how much longer they live after receiving treatment, is captured as part of a metric called quality-adjusted life years (QALYs), where one QALY reflects one year in perfect health. Data related to quality of life was also collected in CheckMate 8HW using a questionnaire filled out by the patients called EQ-5D-3L, which captures mobility, self-care, ability to perform usual activities, pain/discomfort, and anxiety/depression. Improvements in each of these domains is expected to capture the relevant health-related quality of

life benefits a patient would experience from treatment with nivolumab + ipilimumab. Overall, QALYs improved in people who received nivolumab + ipilimumab compared with people who received chemotherapy, reflecting a comparative improvement to patient's length of life and quality of life after receiving treatment.

Results of the economic modelling show that nivolumab + ipilimumab provides a cost-effective alternative to both pembrolizumab and chemotherapy in patients with dMMR/MSI-H, meaning that treatment with nivolumab + ipilimumab offers an acceptable use of NHS resources.

As with all modelling approaches, this analysis contains some limitations including:

- There is no clinical trial directly comparing nivolumab + ipilimumab with pembrolizumab in people with dMMR/MSI-H mCRC. To address this, statistical models were used to estimate how well each therapy improves outcomes for patients relative to one another.
- As outlined previously, the majority of people who received nivolumab + ipilimumab in CheckMate 8HW remained alive after 24 months (2 years) of follow-up. While this is very positive for patients and not uncommon during the appraisal of immunotherapies, it can introduce uncertainty into statistical analyses using this data as assessment of treatment effectiveness relies primarily on the PFS data from CheckMate 8HW.[22,27] However, as shown in CheckMate 142, PFS benefits are linked with strongly improved OS too, benefits that are sustained over a long period.
- As both CheckMate 8HW and CheckMate 142 were open-label trials and participants knew what medicine they were receiving, it is possible that patient-reported outcomes such as health-related quality of life might be influenced. However, key efficacy endpoints such as PFS, OS and ORR should not be affected.
- Both CheckMate 8HW and CheckMate 142 only included patients aged 18 years or older, so evidence in the adolescent population was not obtained from these clinical trials. However, modelling analysis suggests that nivolumab + ipilimumab is expected to provide comparable benefits and risks in both adults and adolescents.[43]

Uncertainties in the model are explored by assessing which variables impact the cost-effectiveness of nivolumab + ipilimumab the most. Across all scenarios tested, nivolumab + ipilimumab presented a cost-effective use of resources compared with pembrolizumab and chemotherapy.

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)

Nivolumab + ipilimumab offers a valuable improvement in delaying disease progression compared with chemotherapy. After 12 months, 79% of patients who received nivolumab + ipilimumab had not experienced disease progression or death, compared with only 21% of the people who received chemotherapy.[36,39] A survival benefit is maintained across subgroups, suggesting that treatment with nivolumab + ipilimumab might work well in people who do not respond to therapies that are currently available.

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

There are not expected to be any equality issues associated with using nivolumab plus ipilimumab to treat dMMR/MSI-H CRC.

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. 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.

Further information on trial data supporting nivolumab+ipilimumab in the dMMR/MSI-H subtype of mCRC, who have not received prior treatment with chemotherapy can be found here:

- CheckMate-8HW: First-Line Nivolumab Plus Ipilimumab Improves PFS Versus Chemotherapy in MSI-H/dMMR mCRC (ascopubs.org)
- Expanded efficacy analysis from CheckMate 8HW - presented at ASCO 2024 (https://meetings.asco.org/abstracts-presentations/231645)
- Xu Y, Liu K, Li C, et al. Microsatellite instability in mismatch repair proficient colorectal cancer: clinical features and underlying molecular mechanisms. eBioMedicine. 2024;103.
- Buchler T. Microsatellite Instability and Metastatic Colorectal Cancer – A Clinical Perspective. Frontiers in Oncology. 2022;12.

Cancer Research UK has produced a video on how immune checkpoint inhibitors work: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/immunotherapy/types/checkpoint-inhibitors

Further information on NICE and the role of patients**:**

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

CTLA-4: cytotoxic T-lymphocyte-associated protein 4: A protein found on the surface of the T-cells in the body.

Chemotherapy: A type of cancer treatment that kills fast growing cells in the body including cancer cells. This is a different type of treatment to immunotherapy.

dMMR: mismatch repair deficient: A loss of function in the DNA mismatch repair system. Tumours that are mismatch deficient can develop MSI-H.

Immune system: A collection of different cells in the body that help defend against illnesses, including cancer.

Immunotherapy: A type of treatment that helps the immune system fight cancer and that acts differently to chemotherapies. This is sometimes called immuno-oncology (I.O). Nivolumab and ipilimumab are examples of immunotherapies.

Intravenous: A treatment method where a needle is inserted into the arm or back of the hand and the treatment slowly passes directly into the blood.

MSI-H: microsatellite high: The presence of a higher number of sequences in tumour DNA compared with normal DNA. Tumours that are mismatch deficient can develop MSI-H.

NIVOLUMAB+IPILIMUMAB: Nivolumab (Opdivo®) + ipilimumab (Yervoy®): A combination immunotherapy for cancer treatment.

OS: Overall survival: The length of time that a patient lives with a disease until their death.

PD-1. Programmed death-1: A protein found on the surface of the T-cells in the body.

PFS: Progression-free survival: The length of time that a patient lives with a disease without it getting worse.

T-cell: A type of cell in the immune system that is involved in fighting infections and illnesses, including cancer. Nivolumab and ipilimumab helps support these cells.

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:

1. Cancer Research UK. Symptoms of advanced bowel cancer. Available from: https://www.cancerresearchuk.org/about-cancer/bowel-cancer/advanced/symptoms-advanced-cancer [accessed on 13/03/24].
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab plus ipilimumab for untreated metastatic colorectal cancer with high microsatellite instability or deficient mismatch repair [ID1136]

Clarification questions

July 2024

File name	Version	Contains confidential information	Date
[ID 1136] Nivo Ipi EAG clarification questions [NoCON].docx	V1	Yes	01/08/2024

Section A: Clarification on effectiveness data

Literature review

A1. Document B (B.2.1) states that clinical searches were originally run in 2021 then updated in 2024. However, Appendix D makes no mention of this (neither are any search strategies restricted by date), but instead describes just one search run in 2024. Please clarify.

Response

This is a typographical error in Document B. The search strategy detail in Appendix D is correct. The search strategies for the clinical SLR did not include a date limiter and were run as a single set of searches from database inception to 10 May 2024.

A2. . The CS says that the target population for the clinical effectiveness SLR is interventions for the 1L treatment of recurrent or metastatic CRC. However, the table says it is dMMR/MSI-H. It appears from the appendices provided that the clinical search was for dMMR/MSI-H, but the economic searches were for recurrent or metastatic CRC**.** Please clarify.

Response

This submission covers the full anticipated marketing authorisation for nivolumab plus ipilimumab (NIVO + IPI). We anticipate that NIVO + IPI will be indicated for the first-line (1L) treatment of adult and adolescent patients, 12 years and older, with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).

The clinical SLRs reflect the anticipated marketing authorisation. As resource use, unit costs and health state utilities should not differ for recurrent or metastatic CRC (mCRC), and the subset of mCRC with dMMR/MSI-H, the economic SLRs searched the broader literature base for data sources.

A3. Please provide additional justification for the studies eligible for inclusion in the SLR but excluded from the CS and model.

Response

Resolved by EAG (Clarification meeting, 17th July 2024). All studies identified in the clinical SLR were included in the company submission.

A4. Please clarify whether any AI or machine learning was used within the SLR, and if so, how it was used.

Response

No, artificial intelligence (AI) or machine learning was used within this SLR.

A5. Please clarify why the PRIME study considered outside the scope of the SLR.

Response

The PRIME study is outside the scope of the clinical SLR as it was conducted with previously untreated patients with mCRC. The focus of this appraisal is previously untreated patients with dMMR/MSI-H mCRC.

Decision problem

A6. Please clarify whether the company are including FOLFOXIRI as a comparator. If not, please provide justification.

Response

Yes, FOLFOXIRI is accounted for in the appraisal. In line with the approach taken in TA709, the cost-effectiveness analysis assumes that the chemotherapy arm of CM8HW reflects the efficacy of all chemotherapy regimens (FOLFOX, FOLFIRI, cetuximab with FOLFOX or FOLFIRI, panitumumab with FOLFOX or FOLFIRI, CAPOX, capecitabine and FOLFOXIRI), with costs weighted to reflect the regimens used in the NHS.

A7. We have reviewed the pembrolizumab SmPC and can see that it is only licensed for use in adults, however, you have included it as a comparator for adolescents as

well. Please provide any evidence you have that this is used off-license in adolescents.

Response

There are no dedicated treatment guidelines for adolescents with MSI-H/dMMR CRC. Clinicians have informed us they treat adolescents as they would treat adults. We therefore included pembrolizumab as a possible comparator in the economic evaluation for adolescents.

Trial design

A8. PRIORITY QUESTION. The dose in cohort 3 in study CM142 appears to be different than other cohorts in this study and from CM8HW. Please clarify whether this is the case and what the impact of this may be.

Response

This is the case, the dose in cohort 3 was nivolumab 3mg/kg every 2 weeks, with ipilimumab 1mg/kg every 6 weeks. This dose was chosen based on data from Phase 1 Checkmate 012, in NSCLC patients, which showed that it led to an acceptable response rate, while limiting AEs. While there is no direct comparative data between the different dosing schedules used in CM8HW and cohort 3 of CM142 in mCRC, there is data from renal cell carcinoma (RCC), which uses the same dosing schedule as mCRC, looking at the effect of an alternative dosing interval of ipilimumab.

In RCC, the PRISM study (Buckley et al. 2019) compared nivo 3mg/kg or 240mg Q2W or 480mg Q4W, and ipi 1mg/kg Q12W (alternative scheduling), with nivo 3mg/kg and ipi 1mg/kg Q3W for 4 doses (standard scheduling), followed by nivo 480mg. Efficacy analysis showed that increasing the interval between ipi doses from 3 weeks to 12 weeks didn't impact the PFS or OS. In the ITT population, the median follow-up time for OS was 32 months (95% CI, 31 to 34) using the Q12W schedule, and 31 months (95% CI, 28 to 37) using the standard schedule. The post-randomization OS estimate at 12 months was 88.3% (95% CI, 81.3 to 92.8) using Q12W scheduling and 84.1% (95% CI, 72.5 to 91.1) using standard scheduling. At 24 months, the OS estimate was 71.3% using Q12W and 73.7% using standard scheduling. Median OS was not reached (NR) in either arm. The trial was not designed to compare the two regimens

directly. Exploratory analysis showed a post hoc unadjusted hazard ratio of 0.93 (95% CI, 0.56 to 1.54). In analysis of the intermediate and poor risk patients, the median OS was 38.5 (95% CI, 27.1 to NR) months in the Q12W arm and NR in the standard arm. The 24-month OS rates were 65.2% and 66.7% in the Q12W and standard arms, respectively.

Based on the above data, it is likely that the correlation between PFS and OS in nivo and ipi treated 1L MSI-H/dMMR patients derived from CM142 data is applicable to patients treated with the CM8HW dosing regimen.

A9. PRIORITY QUESTION. The 2-year stopping rule in study CM8HW could not be found in the SmPC. Please clarify and justify this stopping rule.

Response

In CM8HW, patients were treated with nivolumab and ipilimumab until progressive disease, toxicity, withdrawal of consent, or a maximum of 2 years of treatment. The SmPC provided with the dossier was a draft of the EMA SmPC and contains reference to the stopping rule in the trial in Section 5.1.

A10. Please explain why an open-label design was used in CM8HW.

Response

An open-label design was considered appropriate due to differences in the dosing regimens and associated toxicities across study treatments, facilitating optimal safety assessment. Although CM8HW was an open-label study, BMS was blinded to the aggregated safety and efficacy data by treatment assignments including comparisons between treatment arms. Assessment of the primary end point (PFS per BICR) was objective and assessed by BICR who remained blinded to patient treatment assignment. The specific treatment taken by a participant was assigned using interactive response technology.

A11. Please confirm whether, in the CM8HW and KEYNOTE-177 trials, the investigator's choice of chemotherapy was reported prior to randomisation and was blinded?

Response

In KN177, the chemotherapy to be used was chosen before randomisation (Andre et al., 2020). KN177 was an open label trial and the sponsors, investigator and participants knew the treatment being administered.

In CM8HW, the choice of chemotherapy regimen was declared prior to randomisation and this information was documented in the patient's medical record.

A12. Please confirm whether the local vs centrally tested immunohistochemistry (IHC) and polymerase chain reaction (PCR) for MSI-H was blinded?

Response

BMS was blinded to the results of the centrally tested IHC and PCR, with exception of limited number of the biospecimen team, who have access to central testing results in order to monitor the overall concordance rate between central and local testing. This was done because the primary endpoint was based on centrally confirmed population.

A13. PRIORITY QUESTION. Please provide a list of reasons for not meeting study criteria/ reason no longer meeting study criteria cohort 3 of the CM142 trial (page 89/ table 29).

Response

[redacted] patients no longer met the study criteria for cohort 3 of the CM142 trial. The reasons they no longer met the study criteria are listed below in **Table 1**.

Table 1: Reason no longer meeting study criteria cohort 3 of the CM142

Number of study participants	Reason for no longer meting the study criteria
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

A14. Please provide a list of “lower importance” prognostic variables that were omitted (Appendix N3, table on slide 5).

Response

The lower importance prognostic variables (Goey et al., 2018) that were omitted were:

- Gender
- Race/ethnicity
- Prior radiotherapy
- Stage at first diagnosis
- Tumour differentiation
- Lactate dehydrogenase (LDH)
- Alkaline phosphatase (ALP)
- Carcinoembryonic antigen (CEA)
- Albumin
- Platelet count
- Initially resectable metastatic disease
- Lung-only disease
- Peritoneal disease
- Number of metastases
- Comorbidity or fit versus unfit patient
- Weight/BMI
- Weight loss
- Symptomatic disease

For later-line trials

- Truly refractory versus ‘just discontinued’ prior treatments
- Time from diagnosis mCRC to start of treatment
- Response and PFS on prior treatments
- Time from the last treatment to start of trial

Trial results

A15. Please present the results for those who received nivolumab monotherapy in CM8HW in the same format as the results provided for nivolumab + ipilimumab.

Response

The requested nivolumab monotherapy data from CM8HW are not available at this timepoint, as the trial has not yet reached maturity, and the statistical requirements necessary for robust analysis have not been met. The trial employs a pre-specified statistical testing hierarchy based on the occurrence of a predetermined number of events to ensure statistical validity and meaningful conclusions.

Releasing the NIVO monotherapy results prematurely could compromise the trial's integrity, potentially introducing bias and variability that may lead to misleading interpretations. BMS are committed to maintaining the study's integrity and ensuring the highest standards of scientific rigor, and we are willing to share the requested data when the required statistical thresholds are met. The earliest we anticipate this data being available is [redacted]

A16. Please explain why in CM8HW, around 15% of those in the ITT population were not confirmed dMMR/MSI-H by central testing.

Response

In accordance with the study protocol, patients with MSI-H or dMMR mCRC identified by the local testing which included PCR, IHC or NGS based assays were enrolled into study. 15% of the ITT population were not confirmed dMMR and or MSI-H by central testing.

Of the 202 ITT population in the nivo+ipi arm, 15 % were not centrally confirmed MSI-H/dMMR, including [redacted] with centrally confirmed MSS and pMMR , [redacted] with MSS or pMMR, and [redacted] not evaluable/not tested. Of the 101 ITT population in the chemotherapy arm, [redacted] were not centrally confirmed MSI-H and/or dMMR including [redacted] with centrally confirmed MSS and pMMR and [redacted] not evaluable or not tested. Reasons for unevaluable tests were primarily inadequate/unsuitable sample. Please see **Table 2**.

Table 2 : MSI-H/dMMR status

Characteristics	Nivo+ipi (n = 202)	Chemotherapy (n = 101)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

A17. What proportion of PFS data had to be imputed for CM8HW?

Response

No imputation for missing data for PFS analysis was applied in CM8WH.

A18. PRIORITY QUESTION. How many patients in CM8HW were from the UK and Europe? How may this affect generalisability?

Response

There were two patients enrolled from the UK, but none were randomised to treatment arms. 65.6% of treated patients were from Europe, with a further 5.6% from Australia, and 2.4% from US/Canada.

Although there were no UK patients treated, the majority of patients were from Europe, and treated in comparable healthcare systems, which means the data can be generalised to the UK population. In general, trials conducted predominantly in Europe/N. America/ Australia are considered to have a population that is generalisable to the UK population,

A19. Please explain why BRAF/KRAS/NRAS mutation status is unknown for so many patients in CM8HW?

Response

BRAF/KRAS/NRAS mutation status was collected from the sites based on patient history/information, but collection was not mandatory. In the final analysis of KN177,

the proportion of patients with unknown BRAF/KRAS/NRAS mutation status was [redacted]%, which is comparable to the [redacted]% of patients in CM8HW.

A20. Please provide a list of reasons for exclusion for cohort 3 of study CM142.

Response

The exclusion criteria for cohort 3 of study CM142 were:

1) Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. Cases should be discussed with the medical monitor. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2) Medical History and Concurrent Diseases

a) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

b) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

c) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

d) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

e) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including prior therapy with anti-tumour vaccines or other immuno-stimulatory antitumor agents. Prior treatment with daratumumab or other anti-CD-38 therapies.

f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enrol.

g) Treatment with any chemotherapy, curative intent radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 4). Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

3) Physical and Laboratory Test Findings.

a) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus (ribonucleic acid or HCV antibody) indicating acute or chronic infection.

b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

4) Allergies and Adverse Drug Reaction

a) History of allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

5) Sex and Reproductive Status

a) WOCBP who are pregnant, breastfeeding.

b) Women with a positive pregnancy test at enrolment or prior to administration of study medication.

6) Other Exclusion Criteria.

a) Prisoners or subjects who are involuntarily incarcerated.

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness.

A21. PRIORITY QUESTION. Please provide available OS data (number of events and Kaplan Meier with 95% confidence interval and numbers at risk). We are aware this data is immature; however, it is important that what is available is provided to allow model validation. An absence of OS data increases decision uncertainty for this appraisal substantially.

Response

The overall survival (OS) data from CM8HW are currently unavailable. At this stage, there have been minimal death events, making it premature to release OS data. The company and all stakeholders, remain blinded to these data. The trial employs a pre-specified statistical testing hierarchy based on the occurrence of a predetermined number of events to ensure statistical validity and meaningful conclusions.

Furthermore, since PFS is the primary endpoint of this trial, the OS data, which is a secondary endpoint, will only be tested if the PFS results are statistically significant. Achieving mature OS data may take several years due to the nature of the endpoints and current event rates.

BMS is committed to upholding the highest standards of scientific rigor and maintaining the trial's veracity. The reasons for the data not being available are to

preserve the trial's integrity and to avoid introducing bias that could potentially lead to inaccurate conclusions.

We are prepared to share the requested OS data once the CM8HW trial reaches maturity. At present, the CM142 analysis provides a robust evidence basis for the correlation of PFS and OS in this patient group.

A22. When does the company expect the next analysis from CM8HW to be available?

Response

Due to the delay of progression-free survival (PFS) events for the comparison of Arms B (Nivo=Ipi) vs. A (Nivo monotherapy) all lines, the pre-planned, study-wise final analysis for overall survival (OS), planned to occur around [redacted] from the first participant randomized (which is around [redacted]), is no longer feasible because it will deviate from the study testing strategy. In order to maintain the testing strategy in the pre-planned analysis around [redacted], the study-wise final analysis for OS at the [redacted] mark has been removed and an interim analysis of PFS B vs A in all lines is added to occur at this time.

If PFS B vs A in all lines meets its pre-specified statistical significance in this interim analysis (IA), the secondary endpoints including OS (IA) are allowed to be tested. PFS final analysis time is updated to occur at approximately the [redacted] minimum follow-up of all randomized participants. Overall survival final analysis time is updated to occur at approximately the [redacted] minimum follow-up of all randomized participants.

[redacted]

A23. PRIORITY QUESTION. In Document B, an analysis is provided examining surrogacy between PFS and OS. Please provide the following additional details:

a) **Please provide additional detail as to how this analysis was undertaken, including how censoring was handled.**

Response

Patient-level PFS-OS correlation in various cohorts of CM142 were analysed using the copula method. In summary, a copula function was used to link the PFS and OS survival functions, and estimation of this bivariate model yields information on the strength and nature of the correlation between PFS and OS times, including rank correlation coefficients (Spearman's rho). This approach was chosen for several reasons, including:

1. the method is exact and unbiased in the presence of censoring, unlike simpler non-parametric estimators such as those based on inverse probability of censoring weights. This feature is important since there are many long-term survivors in CM142 who are censored owing to limited follow-up.
2. the method does not require landmarking and thus does not discard any observations for patients who experience very short progression times, of which there are many in CM142.
3. estimates for Spearman's rho, which is an intuitive and common measure of association, are obtained straightforwardly from a fitted copula model.

The copula method has been applied to PFS-OS correlation in many oncology datasets in the academic literature; see, for example, (Emura et al, 2021), for an application to multiple trials in gastric cancer. In the analyses of CM142, multiple choices of copula function were examined to confirm that the measured PFS-OS correlation strength was robust to model specification.

Full details on the approach undertaken to estimate patient-level PFS-OS correlation in CM142 are provided in a recent poster presentation from ESMO GI 2024 (Roodhart et al., 2024).

b) Please provide alternative estimates of surrogacy, including difference in restricted mean survival time and HR comparing OS and PFS.

Response

We have not provided alternative estimates of surrogacy. Study-level PFS-OS correlation in the overall mCRC population, measured by a trial-reported outcome

such as a hazard ratio or difference in restricted mean survival times, has a very limited interpretation in the specific context of CM8HW, since the MSI-H subpopulation of patients with mCRC respond very differently to immunotherapies than the complementary, and much more prevalent, MSS subpopulation. Very few historical studies are specific to the MSI-H subpopulation, and yet PFS-OS correlation in MSI-H mCRC patients may depend strongly on treatment contrast, since patients treated with chemotherapy may benefit substantially from subsequent immunotherapy. Therefore, while study-level PFS-OS correlation in the overall mCRC population helps to gain a complete understanding of the validity of PFS as a surrogate endpoint for OS in mCRC, this analysis has limited relevance to CM8HW and should be interpreted cautiously. Whereas the patient-level PFS-OS correlation analysis of CM142 has a direct correspondence with the expectation for the NIVO and NIVO+IPI arms of CM8HW, since these phase II data are specific to nivolumab-based therapies in patients with MSI-H mCRC.

c) **Please provide within-trial estimates of surrogacy for NIVO+IPI and include parallel analyses in the SoC arm and the NIVO arm to validate.**

Response

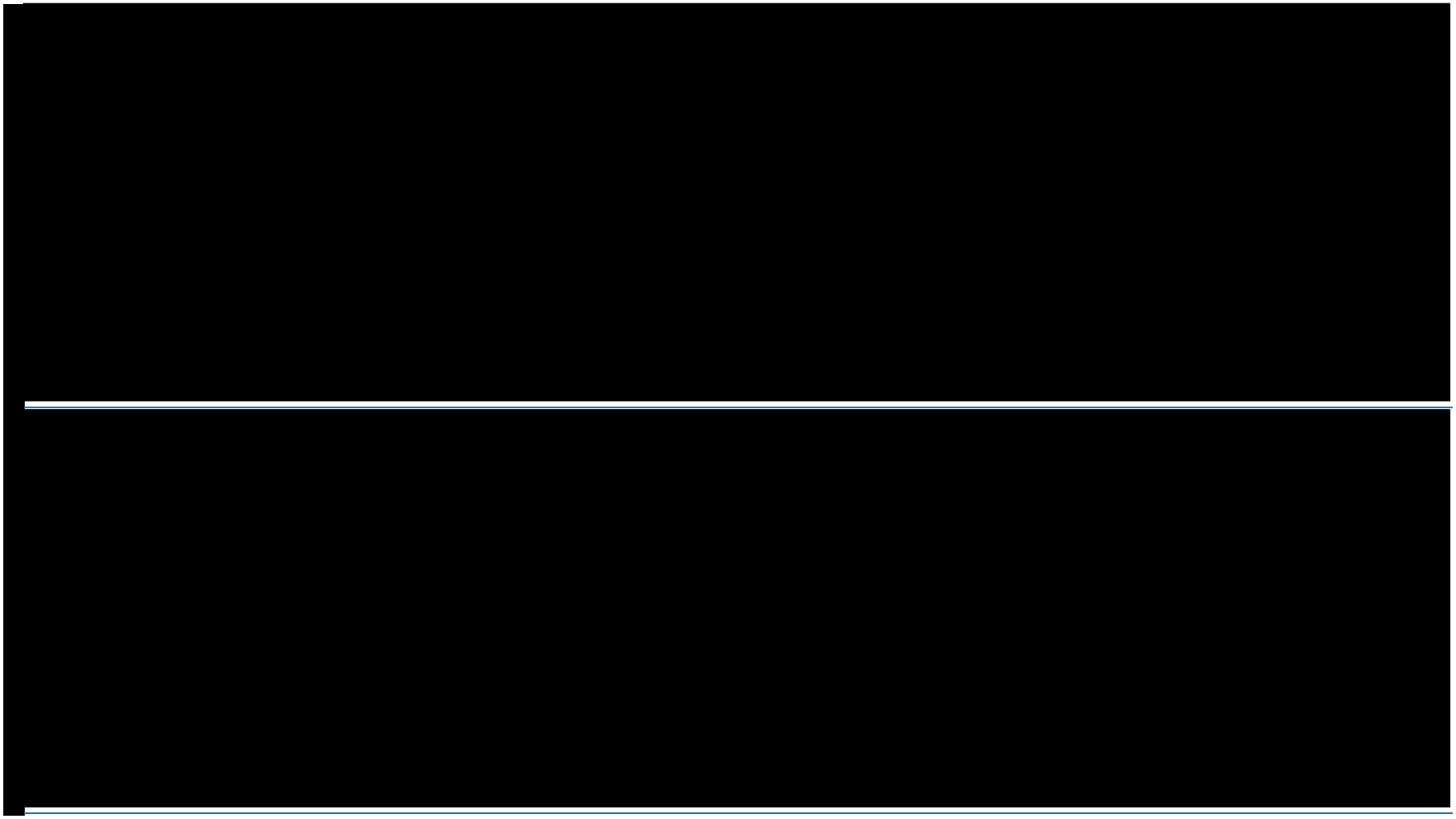
Whilst overall survival (OS) data from CM8HW are currently unavailable (see answer to question A21) it is important to note that the patient-level correlation analysis conducted for CM142, which used the copula method, provides highly relevant information on expected within-trial surrogacy in the NIVO and NIVO+IPI arms of CM8HW, since there is a strong commensurability in the patient populations between the two studies. Moreover, the CM142 analysis is highly valuable in the present context since this study features extended follow-up. In contrast, OS data in CM8HW are currently immature, and therefore any within-trial surrogacy analysis here would be affected by the fact that it is unknown if patients with progressed disease who are censored at the end of follow-up will survive on extended timescales. This feature could lead to poor-quality or uncertain estimates for PFS-OS patient-level correlation from CM8HW.

A24. Please provide a P value(s) for the interaction effect(s) presented for sub-group analysis in Table 29.

Response

The P values for the interaction effects of the sub-group analysis presented in Table 29 of Document B are presented below in **Figure 1**.

Figure 1 : Forest Plot of Treatment Effect on Progression Free Survival per BICR (Primary Definition) - in Pre-Defined Subsets - All First Line Randomized Subjects with Centrally Confirmed dMMR/MSI-H Status in Arm B and C



HR is not computed for subset category with less than 10 subjects per treatment group.
HR = hazard ratio; KME = Kaplan-Meier estimate; N.M.E. = Not meaningful estimate; N.E. = Not estimable.
(1) Unstratified Cox proportional hazard model. HR is Nivo + Ipi over Chemo.
(2) Unstratified Cox proportional hazard model with treatment, subgroup and treatment*subgroup.
interaction to assess the significance of the interaction between treatment and the subgroup.
Excludes data collected on or after first crossover dose date. MSI test per local assessment including both PCR and NGS test.
For local and central MSI/MMR assessment, not available includes both not evaluable and not tested.

For tumor location, other locations unless listed are included in unknown category.
PD-L1 non-quantifiable includes subjects whose PD-L1 status are not evaluable, indeterminate or not available at baseline.

A25. Please provide more information regarding the time to response range (1.2-27.7) in table 28.

a) Please provide additional summary statistics for time to response in the CM142 trial.

Response

Additional summary statistics for time to response in the CM142 trail are included below in **Table 3**.

Table 3: Summary statistics for time to response in the CM142 trial

Summary Statistics	NIVO+ IPI (months)
N	31
Mean	[redacted]
Median	[redacted]
Min	[redacted]
Max	[redacted]
Standard deviation	[redacted]
Lower quartile	[redacted]
Upper quartile	[redacted]

b) Please provide additional RMST analysis with the participant/ data point responsible for the 27.7 in time to response on the CM142 trial, removed.

Response

The restricted mean survival time (RMST) analysis of time to response per BIC and investigator are presented below in **Table *4***. The RMST of progression free survival per BIC and investigator are presented below in **Table *5***.

Table 4: RMST of TTR for all 1L nivo+Ipi treated patients(CM142) excluding the patient with a time to objective response of 27.7

	Time To Response per BICR	Time To Response per Investigator
All patients	[redacted]	[redacted]
Events	[redacted]	[redacted]
Patients %	[redacted]	[redacted]

MEDIAN TTR (MONTHS) (1) (95% CI)	[redacted]	[redacted]
RMST OF TTR AT 60 MONTHS (1) (95% CI)	[redacted]	[redacted]

(1) Based on Kaplan-Meier Estimates

N.A.: Not Available.

Table 5: RMST of PFS for all 1L nivo+Ipi treated patients(CM142) excluding the patient with a time to objective response of 27.7 months

	Progression Free Survival per BICR	Progression Free Survival per Investigator
All patients	[redacted]	[redacted]
Events	[redacted]	[redacted]
Patients %	[redacted]	[redacted]
MEDIAN PFS (MONTHS) (1) (95% CI)	[redacted]	[redacted]
RMST OF PFS AT 60 MONTHS (1) (95% CI)	[redacted]	[redacted]

(1) Based on Kaplan-Meier Estimates
N.A.: Not Available.

A26. Please provide the FP NMA using the identified power solution fitted in the BICR, investigator, and centrally confirmed cohorts for the PFS outcome, and present validation statistics and graphs.

Response

Appendix N1 of the company submission provides the FP NMA using the ITT cohort and assessing PFS per BICR. The FP NMA has been updated using the centrally confirmed cohort and PFS per investigator below.

It should be noted that KEYNOTE-177 only reports PFS per BICR and the ITT cohort. As such, all comparisons are conducted using PFS per BICR for ITT cohort from KEYNOTE-177.

Centrally confirmed cohort PFS per BICR

Results of the fixed-effects FPNMA using the centrally confirmed cohort of CM8HW in place of the ITT cohort of CM8HW in the primary network were consistent with the original analysis and are presented below.

Table *6* is analogous to Table 9 in Appendix N1 of the company submission; with the exception of requiring fewer iterations for satisfactory convergence of the second sensitivity model the results are very similar, with the same ranking per DIC, though absolute differences in DIC are reduced.

Table 7 and **Table 8** are analogous to Table 10 and Table 11 in Appendix N1. As expected, versus SOC, only NIVO+IPI results are modified by the change of informing data. For this comparison, all models demonstrate an increased initial treatment effect in favour of NIVO+IPI, whilst the hazard ratio at month 60 is estimated lower for the Primary and Second sensitivity models, but higher for the first sensitivity model. This is reflected in the hazard ratio of NIVO+IPI versus PEMB, which for the Primary and Second sensitivity models remains in favour of NIVO+IPI with a hazard ratio of 1 falling outside the credible interval at evaluated times up to month 60, whilst for the First sensitivity model the greater uncertainty in parameter inference due to the greater number of degrees of freedom of the model, in conjunction with the slightly modified hazard ratio profile, has resulted in a wider credible intervals that include 1 from month 24, as in the ITT analysis. Median posterior hazard ratios remain in favour of NIVO+IPI.

Figure 2 - **Figure 4** show the hazard ratio profiles, analogous to Figure 5 – Figure 7 in appendix N1. The First sensitivity model showed a greater peak treatment effect for NIVO+IPI versus PEMB (lower hazard ratio) but trended to a similar value by month 60.

Figure 5 to **Figure 7** show the survival predictions based upon the posterior medians of the FPNMA model parameters, analogous to Figure 8 – Figure 10 of appendix N1 of the company submission. All models appear credible.

Table 6: Fixed effect model DIC and Rhat, PFS per BICR, centrally-confirmed cohort (CM8HW)

Selection	Model	DIC	Maximum Rhat	N iterations / samples
Primary analysis	[redacted]	[redacted]	[redacted]	[redacted]
First sensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Second sensitivity	[redacted]	[redacted]	[redacted]	[redacted]

Table 7. PFS hazard ratios versus SOC - Primary network, PFS per BICR, centrally-confirmed cohort (CM8HW)

Selection / model	… vs SOC	HR (95% CrI) at month					
		6	12	24	36	48	60
Primary analysis / Net1_-0.5_-0.5_110	NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First sensitivity / Net1_-0.5_-0.5_111	NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second sensitivity / Net1_-1_0_110	NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8. PFS hazard ratios - NIVO + IPI versus all comparators - Primary network, PFS per BICR, centrally-confirmed cohort (CM8HW)

Selection / model	NIVO + IPI vs …	HR (95% CrI) at month					
		6	12	24	36	48	60
Primary analysis / Net1_-0.5_-0.5_110	SOC	[redacted]					
	PEMB						
First sensitivity / Net1_-0.5_-0.5_111	SOC						
	PEMB						
Second sensitivity / Net1_-1_0_110	SOC						
	PEMB						

Figure 2: PFS hazard ratios - NIVO + IPI versus all comparators - Primary network - Primary model – PFS per BICR, centrally-confirmed cohort (CM8HW)

Figure 3. PFS hazard ratios - NIVO + IPI versus all comparators - Primary network – First sensitivity model – PFS per BICR, centrally-confirmed cohort (CM8HW)

Figure 4. PFS hazard ratios - NIVO + IPI versus all comparators - Primary network – Second sensitivity model – PFS per BICR, centrally-confirmed cohort (CM8HW)

Figure 5. PFS prediction via fractional polynomial models - Primary network - Primary model - PFS per BICR, centrally-confirmed cohort (CM8HW)

Figure 6. PFS prediction via fractional polynomial models - Primary network – First sensitivity model - PFS per BICR, centrally-confirmed cohort (CM8HW)

Figure 7. PFS prediction via fractional polynomial models - Primary network – Second sensitivity model - PFS per BICR, centrally-confirmed cohort (CM8HW)

ITT PFS per investigator

Results of the fixed-effects FP NMA using the PFS per investigator outcome of CM8HW in place of the primary PFS per BICR outcome of CM8HW in the primary network were consistent with the original analysis.

Figure 5 is analogous to Table 9 in Appendix N1 of the company submission; with the exception of requiring fewer iterations for satisfactory convergence of the First and Second sensitivity models the results are very similar, with the same ranking per DIC, though absolute differences in DIC are reduced.

Table 7 and **Table 8** are analogous to Table 10 and Table 11 in Appendix N1. As expected, versus SOC, only NIVO+IPI results were modified by the change of informing data. A very similar hazard ratio profile to the analysis per BICR was observed for this comparison, though absolute values of the hazard ratio were slightly greater. For the NIVO + IPI versus PEMB contrast, this slight modification of the treatment effect resulted in the credible interval of the Primary model crossing 1 at 24 months, the first sensitivity model crossing 1 at 12 months and the Second sensitivity

model crossing 1 at 24 months, but posterior medians all substantially favoured NIVO + IPI.

Figure 8 – **Figure 10** show the hazard ratio profiles, analogous to Figure 5 – Figure 7 in appendix N1. Unlike the analysis per BICR in CM8HW, the hazard ratio for NIVO + IPI versus PEMB monotonically increased in all models, but there was a knee prior to 12 months in all models and the rate of reduction in treatment effect is low after this point. This dramatically higher initial treatment effect had a substantial impact on the relative survival predictions, as show in the following figures.

Figure 11 – **Figure 13** show the survival predictions based upon the posterior medians of the FPNMA model parameters, analogous to Figure 8 – Figure 10 of appendix N1 of the company submission. All models appeared credible within-study. The very low initial hazard ratio of NIVO+IPI versus PEMB in all models resulted in a very low PFS by month 12. In contrast to the BICR outcomes and those reported in KEYNOTE-177, there was no initial period of relatively rapid progression versus platinum-based chemotherapy on NIVO+IPI for investigator-assessed progression. This period of negligible negative treatment effect coincided with the period where the greatest negative treatment effect of PEMB versus SOC was seen, resulting in models that predicted a substantial advantage to NIVO+IPI over this period. Thus, whilst the long-term treatment effect between NIVO+IPI and PEMB was predicted to decrease, the fraction of patients predicted progression-free and able to experience this on PEMB was low relative to those treated with NIVO+IPI.

As in both the CM8HW and KEYNOTE-177 trials the BICR-assessed progressions informed the primary outcome, the apparent lack of exchangeability in the present analysis undermines its credibility and results should not be considered for decision making.

Table 9. Fixed effect model DIC and Rhat, PFS per investigator, ITT cohort (CM8HW)

Selection	Model	DIC	Maximum Rhat	N iterations / samples
Primary analysis	[redacted]	[redacted]	[redacted]	[redacted]
First sensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Second sensitivity	[redacted]	[redacted]	[redacted]	[redacted]

Table 10. PFS hazard ratios versus SOC - Primary network, PFS per investigator, ITT cohort (CM8HW)

Selection / model	… vs SOC	HR (95% CrI) at month					
		6	12	24	36	48	60
Primary analysis / Net1_-0.5_-0.5_110	NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
First sensitivity / Net1_-0.5_-0.5_111	NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second sensitivity / Net1_-1_0_110	NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PEMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11. PFS hazard ratios - NIVO + IPI versus all comparators - Primary network, PFS per investigator, ITT cohort (CM8HW)

Selection / model	NIVO + IPI vs …	HR (95% CrI) at month					
		6	12	24	36	48	60
Primary analysis / Net1_-0.5_-0.5_110	SOC	[redacted]					
	PEMB						
First sensitivity / Net1_-0.5_-0.5_111	SOC						
	PEMB						
Second sensitivity / Net1_-1_0_110	SOC						
	PEMB						

Figure 8. PFS hazard ratios - NIVO + IPI versus all comparators - Primary network - Primary model – PFS per investigator, ITT cohort (CM8HW)

[redacted]

Figure 9. PFS hazard ratios - NIVO + IPI versus all comparators - Primary network – First sensitivity model – PFS per investigator, ITT cohort (CM8HW)

Figure 10. PFS hazard ratios - NIVO + IPI versus all comparators - Primary network – Second sensitivity model – PFS per investigator, ITT cohort (CM8HW)

Figure 11. PFS prediction via fractional polynomial models - Primary network – Primary model - PFS per investigator, ITT cohort (CM8HW)

Figure 12. PFS prediction via fractional polynomial models - Primary network – First sensitivity model - PFS per investigator, ITT cohort (CM8HW)

Figure 13. PFS prediction via fractional polynomial models - Primary network – Second sensitivity model - PFS per investigator, ITT cohort (CM8HW)

A27. Please provide the MAIC(s) in the BICR, investigator, and centrally confirmed cohorts for the PFS outcome.

Response

Please find detailed analyses and reporting for the MAIC using investigator-assessed PFS (INV PFS) (anchored and unanchored) and the MAIC in the centrally confirmed MSI-H/dMMR cohort (cMSI) (anchored and unanchored) in a separate document (BMS 2024a). Generally, the MAICs indicate a similar trend with NIVO + IPI being more favourable than PEMBRO over time, with the analyses based on investigator-assessed PFS being slightly more conservative compared to the MAIC BICR analyses, and the MAIC in the centrally confirmed MSI-H/dMMR cohort presenting more favourable results for NIVO + IPI compared to the ITT population.

Table 12:Additional MAIC analyses

		HR (95% CrI) at month				
		12	24	36	48	60
FP NMA	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anchored MAIC	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anchored MAIC INV PFS	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unanchored MAIC INV PFS	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anchored MAIC cMSI	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unanchored MAIC cMSI	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant HR NMA	NIVO + IPI vs PEMBRO			[redacted]		

INV PFS: investigator assessed PFS; cMSI: centrally confirmed MSI-H/dMMR cohort

A28. PRIORITY QUESTION. The company mention on page 33 that "patients with very advanced disease, in whom progression would rule out further treatment" may be more suitable for chemotherapy based on the results of KN-177. Could the company please define this population and present subgroup analysis for this population in CM8HW?

Response

The patients with very advanced disease, in whom progression would rule out further treatment are not defined by the available KN177 or CM8HW data, therefore providing comparative analysis for this population vs chemo is not possible.

In the analyses of KN177, there were subgroups of patients who did not seem to benefit from pembrolizumab, which may drive the decision to use chemo over pembrolizumab (see **Figure 14** and **Figure 15**). However, subgroup analysis of CM8HW shows that all subgroups benefited from nivo and ipi. Therefore, the decision

of which patients are more suited to chemo will change if nivo and ipi becomes available to the NHS.

Pre-specified subgroup analyses demonstrated consistent benefit of nivo ipi over chemo across all the subgroups (see Table 29 of Document B).

Table 29 (of Document B): CM8HW subgroup analysis for PFS in centrally confirmed population (interim analysis)

		NIVO + IPI		Chemotherapy	
	N	PFS (95% CI)	N	PFS (95% CI)	HR (95% CI)
Age					
< 65	[redacted]	NR [redacted]	[redacted]	5.68 [redacted]	0.19 [redacted]
≥ 65	[redacted]	NR [redacted]	[redacted]	5.85 [redacted]	0.24 [redacted]
≥ 65 and < 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region					
US/Canada/ Europe	[redacted]	NR [redacted]	[redacted]	5.68 [redacted]	0.27 [redacted]
Asia	[redacted]	NR	[redacted]	7.39 [redacted]	0.03 [redacted]
Rest of world	[redacted]	NR [redacted]	[redacted]	6.21 [redacted]	0.16 [redacted]
ECOG PS					
0	[redacted]	NR [redacted]	[redacted]	9.00 [redacted]	0.22 [redacted]
1	[redacted]	NR [redacted]	[redacted]	4.21 [redacted]	0.20 [redacted]
Liver metastasis					
Yes	[redacted]	NR [redacted]	[redacted]	5.85 [redacted]	0.11 [redacted]
No	[redacted]	NR [redacted]	[redacted]	5.36 [redacted]	0.28 [redacted]
PD-L1 status					
≥ 1%	[redacted]	NR [redacted]	[redacted]	3.35 [redacted]	0.11 [redacted]
<1%	[redacted]	NR [redacted]	[redacted]	6.47 [redacted]	0.22 [redacted]
Mutation status					

BRAF/KRAS/NRAS WT	[redacted]	34.30 [redacted]	[redacted]	5.36 [redacted]	0.08 [redacted]
BRAF mutant	[redacted]	NR [redacted]	[redacted]	9.23 [redacted]	0.37 [redacted]
KRAS or NRAS mutant	[redacted]	NR [redacted]	[redacted]	5.68 [redacted]	0.24 [redacted]

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; NA, not available; NIVO, nivolumab; PD-L1, programmed death ligand 1.

Figure 14: KN177 subgroup analysis for OS (Shiu et al., 2023)

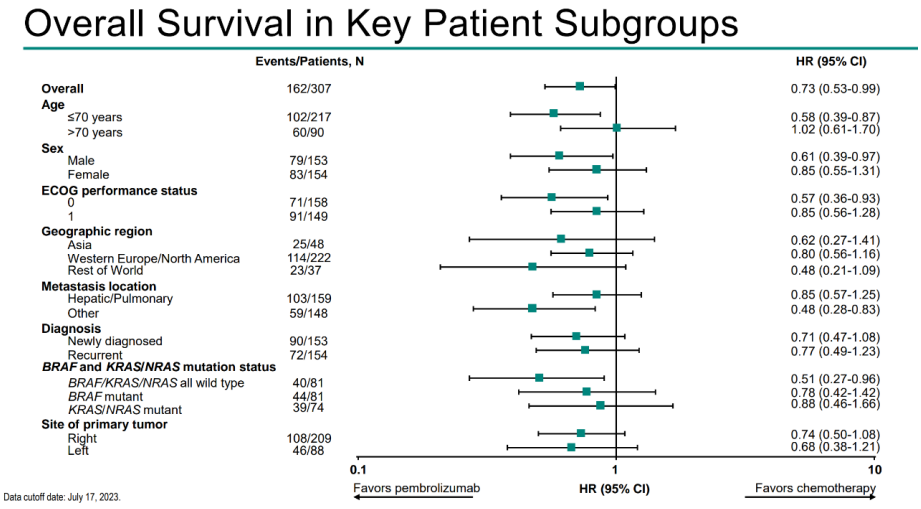
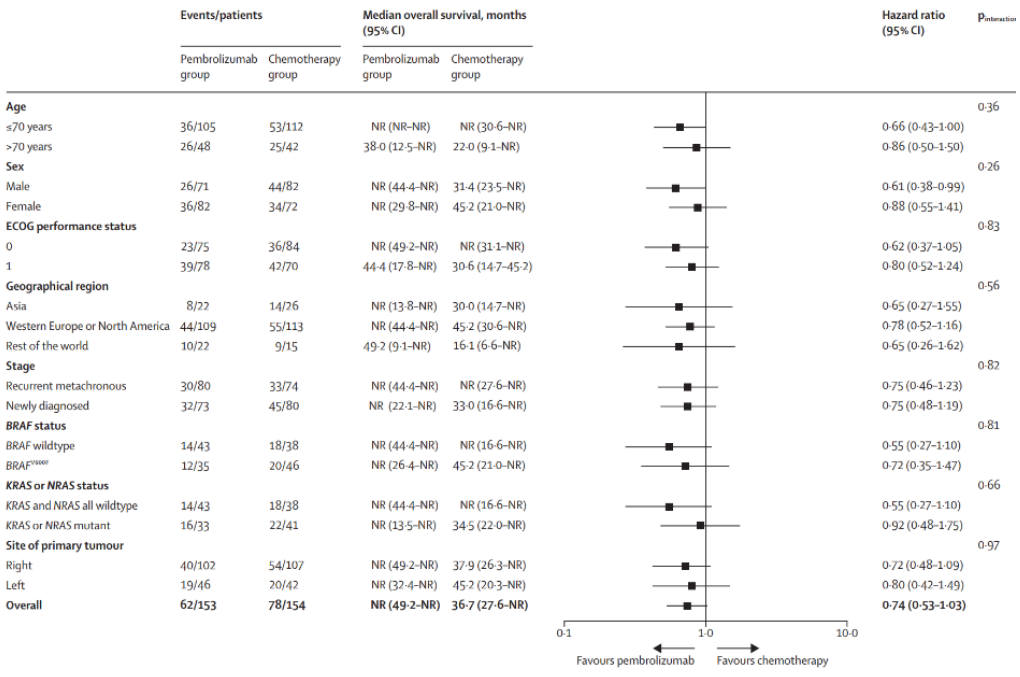


Figure 15: KN177 subgroup analysis for PFS, Final Analysis (Diaz Jr et al, 2022)



A29. PRIORITY QUESTION. Please provide information on the number of patients censored for PFS due to receipt of a subsequent treatment. Please also comment on the appropriateness of using an analysis where PFS is censored for subsequent treatment in the model whilst assuming patients receive subsequent treatment on progression using those PFS curves.

Response In line with the trial protocol, CM8HW patients who received subsequent treatment prior to PFS event (progression or death) were censored for this event. **Table 13** presents an overview of patients censored for PFS due to receipt of subsequent treatment prior to PFS event. In the NIVO + IPI arm, [redacted] patients ([redacted]) received subsequent treatment prior to PFS event compared with [redacted] patients ([redacted]) in the chemotherapy arm (approximately four times higher than the NIVO + IPI arm).

Table 13: CM8HW trial patients that were censored due to subsequent treatment

	NIVO+ IPI N = 202	Chemo N = 101
Received subsequent cancer therapy [b]	[redacted]	[redacted]
Received subsequent systemic therapy	[redacted]	[redacted]
Received subsequent radiotherapy	[redacted]	[redacted]
Received subsequent surgery	[redacted]	[redacted]

[a] Subjects who received subsequent anti-cancer therapy prior to the first on-study scan were censored on the randomization date.
[b] Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy without a prior reported PFS event. Those subjects were censored at the last evaluable tumour assessment prior to/on start date of subsequent anti-cancer therapy

The PFS endpoint definition is standard across oncology clinical trials (FDA, 2015; FDA 2018), including KEYNOTE-177 (NICE, 2012), and was pre-specified as the primary analysis definition for CM8HW. However, it is acknowledged that there is potential for informative censoring, as observed by the high proportion of patients in the chemotherapy arm who switched to receive NIVO + IPI. The CM8HW study included outcomes that support the exploration of uncertainty in the primary PFS definition:

- PFS per BICR using the EMA definition, which does not apply censoring at subsequent anti-cancer therapy. Outcomes are provided in **Figure 16** and are consistent with PFS per BICR applying the primary definition. As can be seen, the impact of censoring is limited in both arms, but primarily impacts the

chemotherapy arm, which benefits from increased survival. However, the benefits of NIVO + IPI are maintained, as observed by a hazard ratio of [redacted], compared with 0.32 (95% CI: 0.23, 0.46) for the primary definition.

- PFS on crossover to NIVO + IPI, defined as time from first crossover dose date to progression or death, whichever occurred first. Outcomes are presented in **Figure 17**.

Within the economic model, use of the CM8HW PFS definition is justified. [redacted] of patients in the chemotherapy arm received a subsequent systemic treatment prior to progression, minimising impact on economic model inputs. Any potential impact favours the chemotherapy arm and disadvantages the NIVO + IPI arm, as pre-progression survival may be extended in the chemotherapy as a result of NIVO + IPI use prior to progression. Further, treatment switching prior to progression will be limited to intolerance or contra-indication in clinical practice, as opposed to patients choosing to switch to a more effective treatment as in CM8HW. As a result, use of PFS and TTP to inform the economic model is reflective of clinical practice.

Figure 16: PFS per BICR per EMA definition

Figure 17: PFS per BICR for crossover cohort receiving NIVO+IPI

A30. Please clarify what you mean by the term ‘maximum clinical benefit’.

Response

In CM142 “maximum clinical benefit” was an optional reason for discontinuation. It was added as a protocol amendment with the rationale that there was accumulating data to suggest that 24 months of PDL1 checkpoint inhibitor treatment may be sufficient for long term benefit.

Subjects who attain all of the following criteria had the option to discontinue treatment:

- Maximum clinical benefit as defined by the investigator
- Minimum 12 months of treatment (in the absence of unacceptable toxicity) after date of first response (PR or CR) if the patient achieved response
- Minimum 24 months between first dose of study treatment and discontinuation for maximum clinical benefit
- No progression since week 12 of study treatment.

Restaging imaging had to be evaluated before the decision was taken to discontinue at maximum clinical benefit. If the subject’s best overall response was stable disease (SD), investigators were encouraged to ensure approximately 24 months of treatment before the decision to discontinue at maximum clinical benefit in order to capture any late responses.

Section B: Clarification on cost-effectiveness data

Literature review

B1. Please explain why the economic SLRs focus on a slightly different population (recurrent or metastatic CRC) from the clinical SLR (dMMR/MSI-H).

Response

The clinical SLRs reflect the anticipated marketing authorisation. As resource use, unit costs and health state utilities should not differ for recurrent or metastatic CRC

(mCRC), and the subset of mCRC with dMMR/MSI-H, the economic SLRs searched the broader population of mCRC for a comprehensive review of the economic literature.

B2. Please explain whether any published/validated search filters used in the economic SLRs.

Response

The search strategies run for the economic SLRs did not include the use of any single published or validated search filters. The search strategy used a bespoke filter designed to ensure all relevant terms were captured.

B3. Please describe and (if necessary) justify any changes made to the economic search strategies between the original (from inception to 2021) and current (2021 to 2024) SLR searches.

Response

There were no changes made to the economic search strategies between the original and current SLRs. The searches run in May 2024 were a re-run of the original search strategies for the purpose of the SLR update. The only addition made to the 2024 search strategies was a date limiter for 01 July 2021 to 17 May 2024.

Modelling analysis

B4. PRIORITY QUESTION. Please present a scenario assuming equal effectiveness for nivolumab using data from CM8HW and pembrolizumab.

Response

The requested nivolumab monotherapy data from CM8HW are not available at this timepoint, as the trial has not yet reached maturity, and the statistical requirements necessary for robust analysis have not been met. The trial employs a pre-specified statistical testing hierarchy based on the occurrence of a predetermined number of events to ensure statistical validity and meaningful conclusions.

Releasing the NIVO monotherapy results prematurely could compromise the trial's integrity, potentially introducing bias and variability that may lead to misleading interpretations. BMS are committed to maintaining the study's integrity and ensuring the highest standards of scientific rigor, and we are willing to share the requested data when the required statistical thresholds are met. The earliest we anticipate this data being available is late [redacted].

Additionally, marketing authorisation for nivolumab monotherapy is not currently being sought. As such, this data can be considered outside the scope of the appraisal.

B5. PRIORITY QUESTION. Which tariff was used for EQ-5D in the model? If it was not the UK tariff please provide updated results.

Response

The UK tariff (Doland, 1997) was used for the EQ-5D in the model.

B6. Please present the results for the weighted mean population by running the scenarios (adult population and adolescent population) and then weighting the scenarios or else please justify the decision to weight based on inputs rather than outputs.

Response

Weighting inputs enables deterministic and probabilistic analyses to be undertaken within the economic model, which cannot be easily undertaken when weighting outputs. However, weighting outputs can be conducted as a scenario, as provided below.

In the company submission, baseline characteristics for the weighted mean population were weighted using the proportion of CRC diagnoses in age 10–19 years versus overall patient cohort (0.098%) (Cancer Research UK, 2018), see Table 94 (Document B) below for the base case ICERs. In line with the EAG's request, the result of weighting the scenarios is provided below in **Table 14**.

Table 94 (document B): Base-case results: weighted population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£331

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYG: life years gained; LYs: life years; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 14: Calculating the outputs of the mean weighted population using the EAG approach (including PAS)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO+IPI	[redacted]	[redacted]			
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£336.10

Costs and QALYs discounted

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Using the different approach to weighting results in negligible effects on the incremental costs and QALYs, consequently having very minor effects on the ICERs.

B7. PRIORITY QUESTION. A generalized gamma model was chosen for the extrapolation of TTP based solely on its low AIC value. Additionally, the visual fit to the nivo+ipi arm is poor. Please present an assessment of the clinical plausibility and long-term data to support this choice and consider whether a more complex model is required to better fit the nivo+ipi arm.

Response

The decision to use a generalised gamma model is detailed extensively in the Company Submission Document B Section B.3.3.1.1 (page 170-171) and in Appendix O Section 3.2.2 (page 31-32). While AIC is considered, others factors assessed are aligned with NICE DSU TSD 14 (NICE, 2011) and include visual inspection of fit to data, log cumulative hazard plots and plausibility of long-term extrapolations.

Additionally, external data was used to validate selections, as detailed in Company Submission Document B Section B.3.13.1.1 (page 273-275) and in Appendix O Section 4.1 (page 64-66). As evidence of the decision process, generalised gamma was selected as most appropriate in the chemotherapy arm, despite a slightly higher AIC compared with lognormal ([redacted] compared with [redacted]). As such, it is incorrect to say that "a generalized gamma model was chosen for the extrapolation of TTP based solely on its low AIC value".

Rationale for survival modelling approach

The survival analysis presented in the company submission is aligned with NICE DSU TSD 14 and 21 (NICE, 2011, 2020). In line with this approach, the following activities were undertaken sequentially:

- Log-cumulative hazard and quantile-quantile plots were assessed.
- As the plots were not parallel, individual models were fitted.
- Standard parametric fits were assessed for suitability.
- Generalised gamma was considered most appropriate as it is a flexible model and able to fit the changing hazard profile, as reflected by goodness of fit statistics (AIC/BIC) and visual assessment of fit to observed data.

More complex approaches, such as spline models and piecewise approaches, are used where standard parametric fits are inappropriate to reflect the data. (NICE, 2011, 2020). While complex flexible models are able to fit observed data well, these models reduce to standard Weibull, lognormal or log-logistic models beyond the trial period (Latimer and Adler, 2022). Depending on where knots are placed within a spline, this may limit data available to inform the extrapolation phase and reduce face validity. As such, a complex model might be preferred if the hazard function is continuously varying, rather than one in which the early data are progressively less influential over time, as with a spline.

It is acknowledged that other standard parametric fits were less able to capture the changing hazard profile, with a resulting impact on visual fit to observed data and goodness of fit statistics. By contrast, the generalised gamma had the lowest AIC

([redacted]) by a large margin (log logistic [redacted], log normal [redacted]). Additionally, the generalised gamma was also the only model that reflected the increased hazards between month 0 and month 6 in the observed NIVO + IPI arm, as well as the reduced hazards over time. Log-logistic and lognormal fits were also considered potentially plausible, but the fits were not considered as appropriate as generalised gamma, based on observed fit to the data and goodness of fit data.

In addition to being the best fit in terms of AIC and visual assessment of fit to observed data in the NIVO + IPI arm, the generalised gamma fit was also chosen for the chemotherapy arm. Similarly, as part of the ITC, generalised gamma was the best fit for pembrolizumab, based on digitised KEYNOTE-177 Kaplan-Meier data. Based on guidance from NICE DSU TSD 14 (NICE 2011), "when parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model". Therefore, using the generalised gamma for NIVO + IPI follows this best practice guidance.

Assessment of clinical plausibility

The parametric survival curves were presented to a UK advisory board and a global advisory board that included clinical experts and health economists, where standard parametric fits were considered plausible, although no specific extrapolation was preferred. However, the experts stressed the importance of external validation.

External validation of survival curves was assessed using data from CheckMate 142 (Company Submission Document B Section B.3.3.1.1.2 Table 57), KEYNOTE-177 and Tougeron et al., (2020) (Company Submission Document B Section B.3.3.1.2.2 Table 60). Validation of these survival curves is reproduced below, adapted to account for EAG request in B8 and B9. Additionally, economic model outcomes were assessed for plausibility using data from CheckMate 142 and KEYNOTE-177 (Company Submission Document B Section B.3.13.1).

The estimates of the median TTP, one-year, two-year, and five-year progression-free probability generated by the extrapolation of the CM8HW NIVO + IPI arm were compared against PFS data from CM142 Cohort 1 (2L+ mCRC receiving NIVO monotherapy), Cohort 2 (2L+ mCRC receiving NIVO + IPI) and Cohort 3 (1L mCRC receiving NIVO + IPI), as described in **Table 15**. Observed TTP in CM142 cohorts 2

and 3 was comparable with all parameterisations at year 1, but generalised gamma was the best fit at years 2 and 3. This comparison demonstrates that the generalised gamma extrapolation has the most face validity. Lognormal and log-logistic extrapolations can be considered highly conservative but may still be plausible.

The extrapolated TTP estimates for the CM8HW chemotherapy arm were validated against PFS outcomes from the published literature, i.e., Tougeron et al., (2020) and chemotherapy PFS data from KN-177 published by Diaz et al., (2022). TTP and PFS cannot be considered interchangeable, as TTP is defined as time from randomisation to progression with censoring for death events whereas PFS is defined as time from randomisation to progression or death. As such, PFS will be expected to be lower than TTP. However, as mortality is low prior to progression, PFS can be used to assess face validity of TTP estimates. As outlined in Table 60 (Document B)**.**, the median estimated TTP for the CM8HW chemotherapy arm is relatively similar to the estimated value in both validation sources and lie within the 95% CIs of both validation estimates. With regards to the estimated landmark survival values, the 95% CI of all 3-year CM8HW extrapolations encompass the estimated 3-year PFS from KN-177 (Diaz et al., 2022). At 5-years, the generalised gamma extrapolated fit TTP for CM8HW validates the best to KN-177 (Diaz et al., 2022).

Table 15: Comparison of landmark survival values for CM8HW NIVO + IPI TTP extrapolation versus CM142 observed values

		Median, years (95% CI)	1-year progression-free	2-year progression-free	5-year progression-free
CM8HW NIVO + IPI	Observed TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic TTP	[redacted]	[redacted]	[redacted]	[redacted]
CM142[7,8]	Cohort 1 (2L+ NIVO) TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Cohort 2 (2L+ NIVO + IPI) TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Cohort 3 (1L NIVO + IPI) TTP	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IPI, ipilimumab; NE, not evaluable; NIVO, nivolumab; NR, not reached; PFS, progression-free survival; TTP: time to progression.

Table 16: Comparison of landmark survival values for CM8HW chemotherapy TTP extrapolation versus Tougeron et al., (2020) and KN-177

		Median, years (95% CI)	1-year progression-free	3-year progression-free	5-year progression-free
CM8HW chemotherapy	Observed TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic TTP	[redacted]	[redacted]	[redacted]	[redacted]
Tougeron et al. (2020)	1L chemotherapy PFS	6.0 (5.0, 7.8)	-	-	-
KN-177	1L chemotherapy PFS	8.2 (6.2, 10.3)	-	13%	8%

TTP defined as time from randomisation to progression, censored at subsequent treatment or death events. PFS defined as time from randomisation to progression or death, censored at subsequent treatment. PFS will be expected to be lower than TTP. However, as mortality is low prior to progression, PFS can be used to assess face validity of TTP estimates.

Abbreviations: CI, confidence interval; NR, not reached; PFS, progression-free survival; TTP, time to progression.

Alternative survival models

All alternative standard parametric fits were assessed in the economic model as scenario analyses, as outlined in Company Submission Document B Section B.3.9.3.2.2 and Section B.3.9.3.2.3, including extrapolations lacking clinical face validity. These scenarios demonstrate that even implausibly conservative extrapolations did not greatly impact cost-effectiveness conclusions.

Table 17: Scenario analysis: alternative NIVO + IPI TTP extrapolations - adult population (with PAS)

NIVO + IPI TTP extrapolations (ordered by AIC)	PEMBRO			Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
Generalised Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£332
Lognormal	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£268
Log-logistic	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£192
Gompertz*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£562
Weibull	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£337
Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£414
Exponential*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£144

*Clinically implausible extrapolations, as outlined in Company Submission Document B Section B.3.3.1.1 .
Abbreviations: AIC, Akaike information criterion; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TTP, time to progression

Table 18: Scenario analysis: alternative chemotherapy extrapolations - adult population (with PAS)

Chemotherapy TTP extrapolation (ordered by AIC)	NIVO + IPI versus Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
Lognormal	[redacted]	[redacted]	£1,388
Generalised Gamma	[redacted]	[redacted]	£322
Log-logistic	[redacted]	[redacted]	£1,328
Gamma	[redacted]	[redacted]	£1,900
Exponential	[redacted]	[redacted]	£1,645
Weibull	[redacted]	[redacted]	£1,840
Gompertz	[redacted]	[redacted]	£378

Abbreviations: AIC, Akaike information criterion; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TTP, time to progression

More complex models in the form of 1- and 2-knot spline models were originally not considered, as the standard parametrisations were considered appropriate. However, six spline models have been investigated and compared to the generalised gamma fit. ?? summarises the AIC and BIC values of the standard parametric fits alongside six spline models fit to the CM8HW NIVO + IPI TTP data. While generalised gamma was the lowest AIC and BIC among the standard parametric models, the 2-knot spline models have lower AIC and BIC statistics.

Table 19: CM8HW NIVO + IPI TTP AIC values – standard parametric and spline models (lowest AIC in bold)

TTP	CM8HW NIVO + IPI AIC	CM8HW NIVO + IPI BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]
Log normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Spline hazard 1	[redacted]	[redacted]
Spline hazard 2	[redacted]	[redacted]
Spline odds 1	[redacted]	[redacted]
Spline odds 2	[redacted]	[redacted]
Spline normal 1	[redacted]	[redacted]
Spline normal 2	[redacted]	[redacted]

Extrapolations for the six spline models compared against the generalised gamma can be found in **Figure 18** and **Figure 19**. The generalised gamma was comparable in both the observed and extrapolated time frame to the single knot splines and the two-knot hazard spline. The two-knot normal spline and two-knot odds spline fit provide a tighter fit to the early part of the observed period. However, as noted above, this can be expected of spline models and this should be viewed in the context of the limitations noted above and in the published literature (Latimer, et al., 2022).

Figure 18: CM8HW NIVO + IPI TTP spline fits to end of trial period

Figure 19: CM8HW NIVO + IPI TTP spline fits beyond trial period

Table *20* summarises the AIC and BIC values of the six spline models fit to the CM8HW chemotherapy TTP data. Several spline models have AIC slightly lower than that for the generalised gamma extrapolation (687.4); however, all are broadly similar.

Table 20: CM8HW chemotherapy TTP AIC values – standard parametric and spline models (lowest AIC in bold)

TTP	CM8HW chemotherapy AIC	CM8HW chemotherapy BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]
Log normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Spline hazard 1	[redacted]	[redacted]
Spline hazard 2	[redacted]	[redacted]
Spline odds 1	[redacted]	[redacted]
Spline odds 2	[redacted]	[redacted]
Spline normal 1	[redacted]	[redacted]
Spline normal 2	[redacted]	[redacted]

Extrapolations for the six spline models compared against the generalised gamma can be found in **Figure *20*** and ***Figure 21***. The generalised gamma was comparable with all spline models.

Figure 20: CM8HW chemotherapy TTP spline fits to end of trial period

Figure 21: CM8HW chemotherapy TTP spline fits beyond trial period

A scenario analysis was undertaken using the 2-knot odds spline model for both NIVO + IPI and chemotherapy. This survival curve was chosen as it provided a closer fit to observed NIVO + IPI data from CM8HW and provided one of the more optimistic fits for the chemotherapy arm.

Scenario analysis outcomes are provided in **Table 21**. As can be seen, in the NIVO + IPI arm, LYs and QALYs are decreased versus the base case analysis (versus LYs and versus QALYs), while costs are slightly increased versus). However, similar impacts are observed in comparator arms, so that impacts on the ICER are limited and cost-effectiveness conclusions are unchanged.

Table 21: Scenario analysis: 2-knot odds spline TTP (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs			
Total LYs			
Total QALYs			
Incremental QALYs versus NIVO + IPI			
Incremental costs versus NIVO + IPI (£)			
ICER versus NIVO + IPI (£/QALY)	-	Dominant	£357

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B8. PFS data from CM142 is being used to assess the face validity of TTP extrapolation from CM8HW (despite PFS and TTP not being interchangeable). Please use the same outcome for clinical validation to ensure a proper like-for-like comparison and improve reliability of the results.

Response

Please find below the median TTP for all cohorts in CM142, as well as the 1-year, 2-year, and 5-year progression-free probability. These landmark estimates can be used for clinical validation of CM-8HW outcomes in place of PFS estimated from Cohorts 1, 2, and 3 in CM142. However, please note that, as outlined in response question to B10, PFS and TTP outcomes from these trials are relatively comparable and therefore the face validity checks currently performed using PFS data from CM142 and TTP from CM8HW still hold, given that the PFS data from CM142 is very similar to the TTP data from CM142 included in the table below.

Table 22: Median TTP for all cohorts in CM142

	Median, years (95% CI)	1-year progression-free	2-year progression-free	5-year progression-free
Cohort 1 (2L+ NIVO) TTP	[redacted]	[redacted]	[redacted]	[redacted]
Cohort 2 (2L+ NIVO + IPI) TTP	[redacted]	[redacted]	[redacted]	[redacted]
Cohort 3 (1L NIVO + IPI) TTP	[redacted]	[redacted]	[redacted]	[redacted]

Table 23: Comparison of landmark survival values for CM8HW NIVO + IPI TTP extrapolation versus CM142 observed values

		Median, years (95% CI)	1-year progression-free	2-year progression-free	5-year progression-free
CM8HW NIVO + IPI	Observed TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic TTP	[redacted]	[redacted]	[redacted]	[redacted]
CM142 TTP	Cohort 1 (2L+ NIVO) TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Cohort 2 (2L+ NIVO + IPI) TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Cohort 3 (1L NIVO + IPI) TTP	[redacted]	[redacted]	[redacted]	[redacted]

CM142 cohort 2 and 3 (1L NIVO + IPI) TTP was higher than TTP predicted by all CM8HW extrapolations at years 1, 2 and 5, indicating that all extrapolations may be slightly conservative during this period.

TTP for the CM142 Cohort 1 (2L+ NIVO monotherapy) was lower at all time points compared with TTP from CM8HW NIVO + IPI treatment arm extrapolations, as can be expected based on regimen and treatment history.

This comparison demonstrates that the generalised gamma extrapolation has the most face validity. Lognormal and log-logistic extrapolations can be considered highly conservative but may still be plausible. More conservative extrapolations, such as exponential, gamma, Weibull and Gompertz, appear to lack face validity at five years.

B9. Please provide the 95% confidence intervals for the observed landmark survival values from CM142 for each of the three cohorts in Table 57.

Response

95% confidence intervals from the relevant database locks have been added to Table 57 (document B) below as requested.

Table 57 (of Document B). Comparison of landmark survival values for CM8HW NIVO + IPI TTP extrapolation versus CM142 observed values

		Median, years (95% CI)	1-year progression-free	2-year progression-free	5-year progression-free
CM8HW NIVO + IPI	Observed TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic TTP	[redacted]	[redacted]	[redacted]	[redacted]
CM142[120,121]	Cohort 1 (2L+ NIVO) PFS	1.2	[redacted]	[redacted]	34%
	Cohort 2 (2L+ NIVO + IPI) PFS	NR	[redacted]	[redacted]	[redacted]
	Cohort 3 (1L NIVO + IPI) PFS	NR	[redacted]	[redacted]	[redacted]

B10. Please share the data from KN-177 used to support the assumption that the HR between treatments for PFS would be approximately comparable with the HR of TTP.

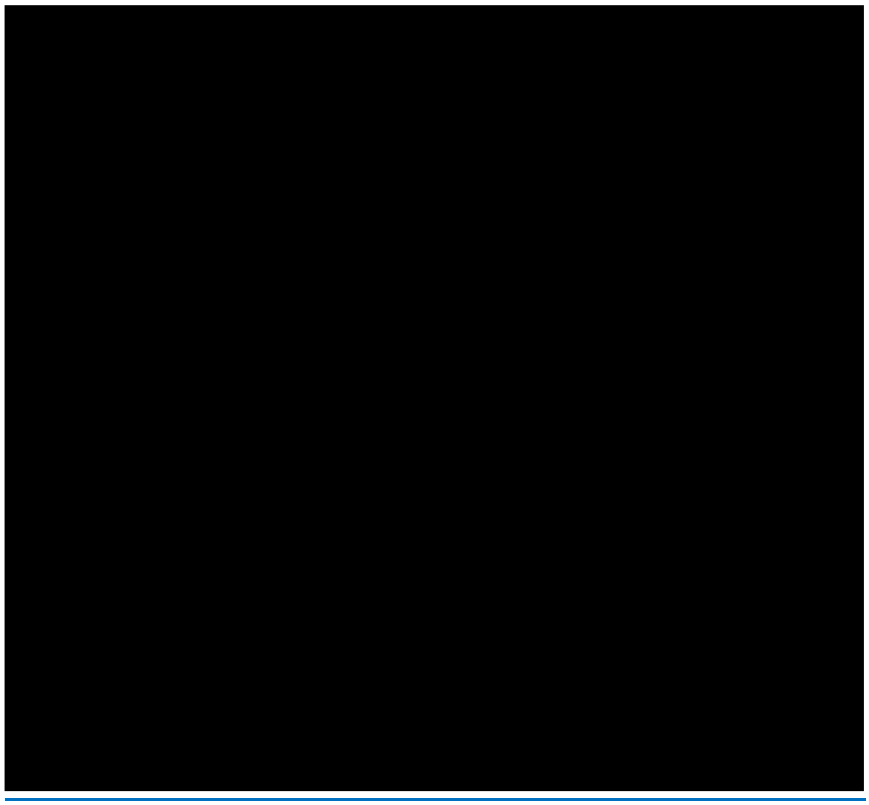
Response

To our knowledge, there is currently no data on TTP published for KN-177, therefore no TTP data could be used within the model and the assumption of comparable HRs for PFS and TTP could not be tested within this trial.

However, we assessed this assumption within CM142 and found that TTP and PFS were similar for the Nivo monotherapy (C1 in CM142) and Nivo + Ipi (C2 and C3 in CM142) arms, as shown in **Figure *22*** and **Figure *23*** below. Thus, we assumed that the HR of PFS would be approximately comparable with the HR of TTP for both Nivo monotherapy and Nivo + Ipi.

Figure 22: KM curves of PFS versus TTP for the Nivo monotherapy arm in CM142

Figure 23: KM curves of PFS versus TTP for the Nivo + Ipi arm in CM142



Furthermore, a similar assumption has been made to inform the health state transitions for non-trial comparators in the economic model the NICE TA709 (NICE, 2012), see table 37 in NICE TA709).

B11. Please provide the PrePS data from the CM142 study as mentioned in the submission.

Response

PrePS from CM142 is provided within Document B Section B.3.9.3.1.2 and Appendix O Section 3.2.4 of the company submission. Additionally, this data has been used within the economic model as a scenario analysis, where impact was limited. This has been reproduced below for ease of reference.

There was a total of 164 patients used to inform this analysis (Cohort 2 [2L+ NIVO + IPI]: 119 patients; Cohort 3 [1L NIVO+IPI]: 45 patients), all of which received NIVO + IPI (***Figure 24***). The median time to death was not reached and the one-year survival probability was [redacted] (95% CI: [redacted]).

Figure 24: CM142 cohorts 2 and 3 pre-progression survival Kaplan-Meier data

As previously mentioned, there were few events so that the data can be considered extremely immature and should be viewed with caution, as evidenced by ***Figure 25***.

As previously described for the TTP survival analysis, the best model fit was selected based on the model selection algorithm outlined in Palmer et al. (2023) as well as via statistical tests such as AIC. The lognormal model is recommended based on low AIC value and plausible long-term extrapolation. For this scenario analysis, the economic model applies this data in addition to general population mortality.

Figure 25: CM142 cohort 2 (2L+ NIVO + IPI) and 3 (1L NIVO + IPI) PrePS standard parametric fits beyond trial period

Results are provided in **Table 24**. Total LYs and QALYs are decreased across all modelled treatment arms due to increased deaths from the progression-free state. However, this results in lower resource use for NIVO + IPI and PEMBRO, so that ICERs are relatively unchanged versus PEMBRO and are dominant versus chemotherapy.

Table 24: Scenario analysis - CM142 for PF-D transition - adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	Dominant

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B12. PRIORITY QUESTION. The economic model assumes equal TTD for PEMBRO and NIVO + IPI, citing the similar duration of therapy values from CM8HW and KN-177. Please adjust for differences in TTD using the chemotherapy arm in both trials.

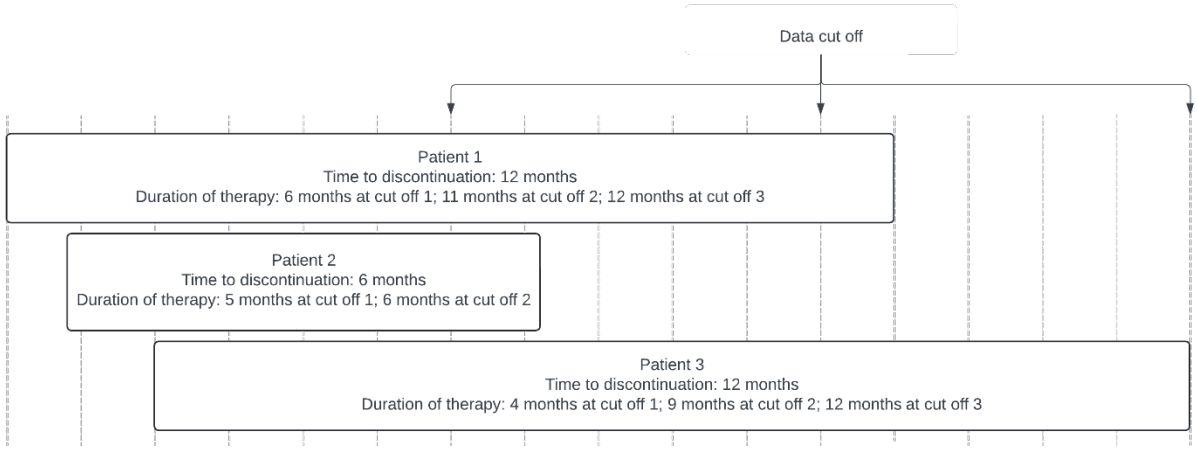
Response

It is not possible to provide a robust analysis to address this question.

Time on treatment within the economic model is informed by time to treatment discontinuation (TTD) defined as the time from first dose date to time of last dose date, which included all study therapies within the multi-agent regimens. Time to treatment discontinuation was summarised using Kaplan-Meier methodology, where the last dose date was the event date for those subjects who were off study therapy and patients who were still on study therapy were censored on their last dose date.

No time to discontinuation data is reported for KEYNOTE-177. Duration of therapy, as reported by KEYNOTE-177, is defined as time from first dose date to last dose date but does not include censoring of patients who were still on study therapy at last dose date. As such, duration of therapy does not reflect that treatment may continue following data cut off and is impacted by duration of follow up and proportion of patients with ongoing treatment at time of data cut off. A simplified depiction of the difference between duration of therapy and time to treatment discontinuation is provided in ***Figure* 26**. Given the difference in definition, use of time to discontinuation data to inform the economic modelling is best practice.

Figure 26: Simplified overview of time to discontinuation versus duration of therapy



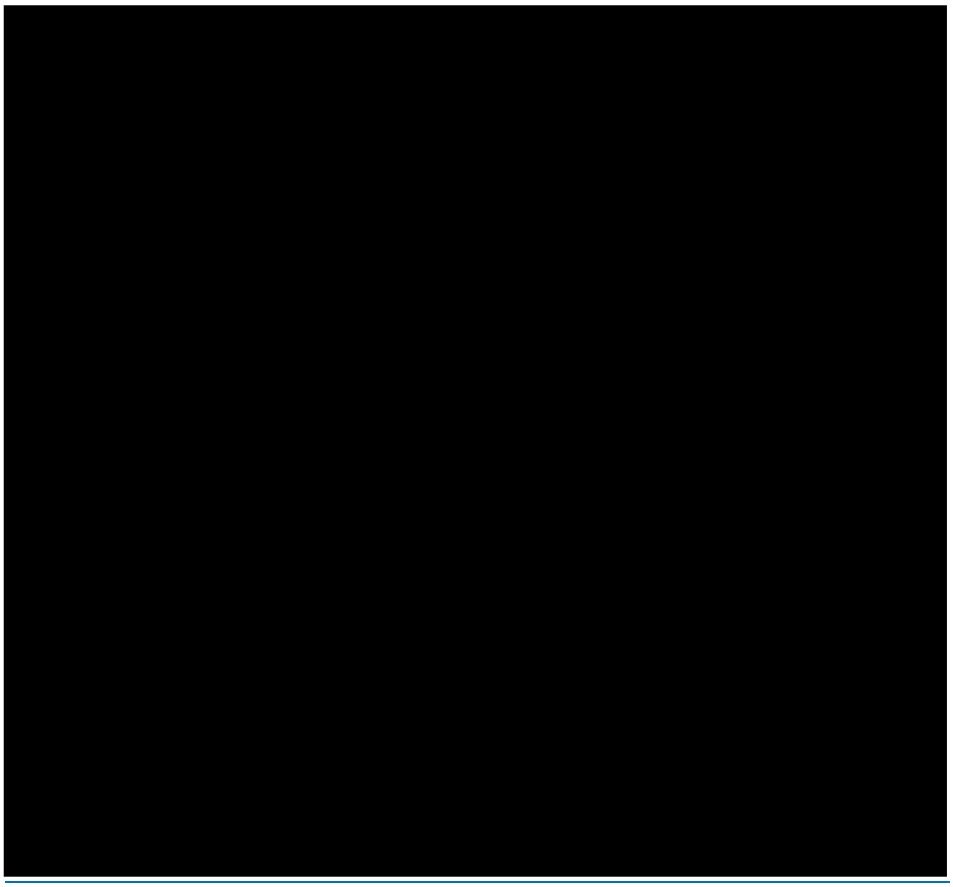
As of the KEYNOTE-177 February 2020 data cut off (minimum follow-up: 24 months; median time from randomisation to data cutoff: 32·4 months; interquartile range: 27·7–37·8 months), two patients (1.3%) in the pembrolizumab arm and 5 patients (4.2%) in the chemotherapy arm were still receiving study treatment. By comparison, at CM8HW data cut off (minimum follow up: 6.1 months; median time from randomisation to data cutoff: 31.5 months; interquartile range: 19.9–38.2 months), [redacted] patients ([redacted]) in the NIVO + IPI arm and [redacted] patients ([redacted]) in the chemotherapy arm were still receiving treatment. These patients have a large impact on the difference between duration of therapy and time to discontinuation, as can be seen in **Table 25**, with censors shown on **Figure 27**.

Given the difference in proportion of patients with ongoing treatment at time of data cut off and the proportion of patients with short follow-up, **it is not appropriate to quantitatively compare duration of therapy between CM8HW and KEYNOTE-177**. These data are provided within the company submission only to inform an assessment of face validity of the assumption of equivalent time to discontinuation between pembrolizumab and NIVO + IPI. As mentioned above, no time to discontinuation data are available from KEYNOTE-177.

Table 25: Comparison of duration of therapy and time to treatment discontinuation within CM8HW

	NIVO + IPI (N = 200)		Chemotherapy (N = 88)	
	Duration of therapy	Time to treatment discontinuation	Duration of therapy	Time to treatment discontinuation
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max (months)	[redacted]	[redacted]	[redacted]	[redacted]

Figure 27: CM8HW TTD KM data



Abbreviations: IPI, ipilimumab; KM, Kaplan-Meier; NIVO, nivolumab; TTD, time to treatment discontinuation

It is acknowledged that patients in the CM8HW chemotherapy appear to be discontinuing treatment earlier than in KEYNOTE-177. However, this can be expected, as patients are more likely to crossover to receive immunotherapy in the second-line setting. Both NIVO + IPI and pembrolizumab were launched in multiple countries in the second-line CRC setting during the CM8HW enrolment period, which was not the case while KEYNOTE-177 was ongoing. In support of this, of the 101 patients in the

chemotherapy cohort, [redacted] patients crossed over to NIVO + IPI, with an additional [redacted] patients receiving an anti-PD-L1 or anti-PD-1 outside of the study protocol (BMS, 2024b). As a result, the difference in duration of chemotherapy treatment is unlikely to impact on the face validity of assuming equivalent time to treatment discontinuation between NIVO + IPI and pembrolizumab.

B13. Please clarify why the economic model uses naïve AE data and not the incidence of AEs reported in the NMA? Please consider revising the model to use the NMA.

Response

The FP NMA AE outcomes provide high quality evidence but remain subject to considerable uncertainty. Across all individual AEs, the credible interval is inclusive of 0, indicating no significant difference between NIVO + IPI and pembrolizumab. Further, outcomes have face validity compared to AE incidence inputs into the FP NMA. However, all credible intervals are very broad, driven by the low number of events and relatively large differences between the chemotherapy arms of CM8HW and KEYNOTE-177. It is unclear if these differences are driven by differences in duration of treatment or underlying chemotherapy composition, such as increased use of bevacizumab in KEYNOTE-177.

The TA709 economic model applied inputs derived from an NMA for all AEs grade ≥3, applied to individual AE rates for SOC to derive rates for CAPOX and FOLFOX + panitumumab. However, this approach does not reflect the potential for differential treatment impact on individual AEs and assumes treatment impacts all AEs similarly, which may lack face validity.

By contrast, use of the naïve AE data is more transparent, allowing reviewers to verify and question values.

B14. The economic model uses pooled utility data for the progressed disease health state justified by "poor completion rates and censoring following subsequent treatment."

Please provide a scenario where the analysis is re-run by counting subsequent treatment as an event for progression, and then apply the results of the arm-specific analysis.

Response

An analysis was conducted where patients who switched treatment were removed from the PF utility value. Values are provided in **Table 26** below.

Results are provided in **Table 27**. As can be seen, total LYs and QALYs are increased across all modelled treatment arms; however, NIVO + IPI maintains a benefit over PEMBRO and chemotherapy. As a result, ICERs remain below a £30,000/QALY willingness-to-pay threshold.

Table 26: Utility values applied for base case analysis and scenario analysis, with comparison to previous HTAs

		Progression-free	Progressed
Base case analysis	NIVO + IPI/PEMBRO	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
Scenario analysis	NIVO + IPI/PEMBRO	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
TA709 (N-177)	PEMBRO	0.843	0.730
	Chemotherapy	0.787	0.730
TA439	Cetuximab, panitumumab and chemotherapy	0.767	0.64

Table 27: Scenario analysis: alternative utility values - adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	£315

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B15. PRIORITY QUESTION. Please provide the model projections for OS compared to KM curves for:

- **Both arms in the KN-177 trial,**
- **The OS data from the CM214 study for nivo+ipi,**
- **The OS data from the CheckMate 8HW study for all 3 arms.**

Response

Figure 28 and **Figure 29** show the comparisons for the KEYNOTE-177 and CM142 respectively. The third request cannot be fulfilled as overall survival data from CM8HW is not available for analysis at this time.

In the comparison against KEYNOTE-177, it should be recalled that the SOC arm of this trial demonstrated higher PFS than the SOC arm of CheckMate-8HW. As the reference PFS models in the economic model are based on CM8HW, this implies that PFS for SOC and thus PEMBRO should be lower than observed in KEYNOTE-177, and it would be expected that OS would be similarly modified.

In the comparison against CM142, data across cohorts have been pooled, i.e., patients with a variety of treatment experience are represented. Nevertheless, the long-term OS rate is commensurate with observation.

Figure 28: Model OS predictions overlaying KEYNOTE-177 trial observed OS

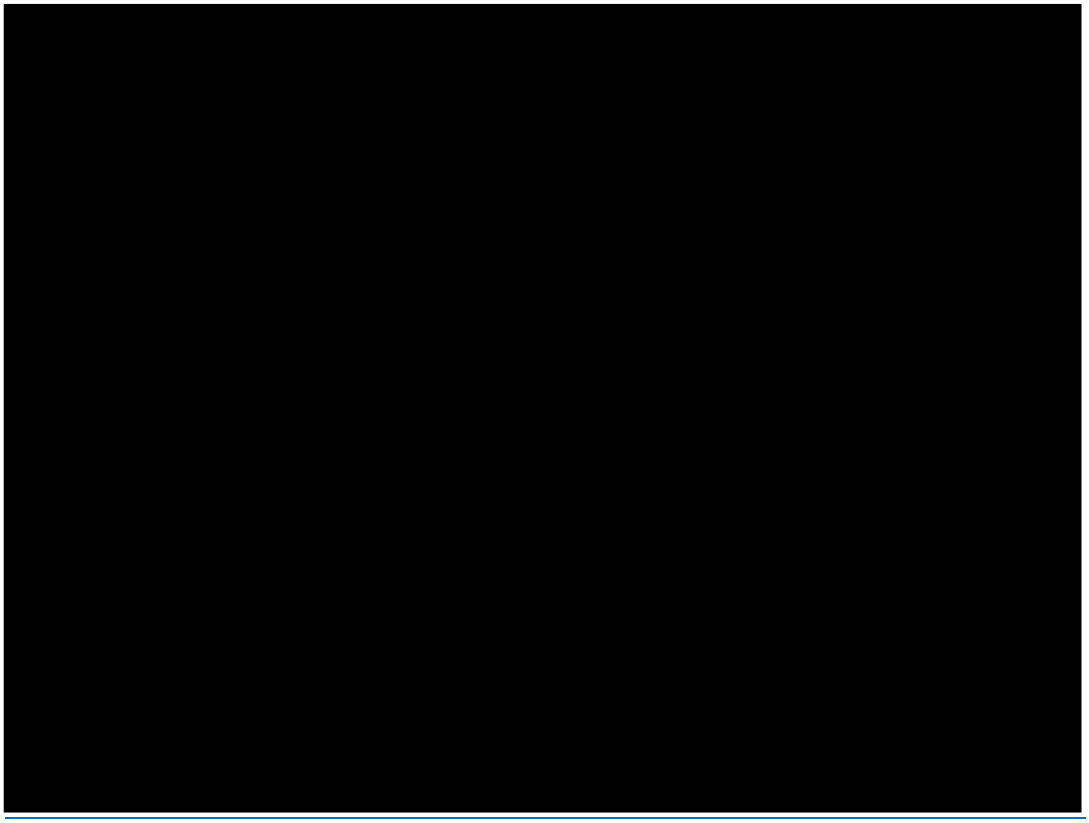
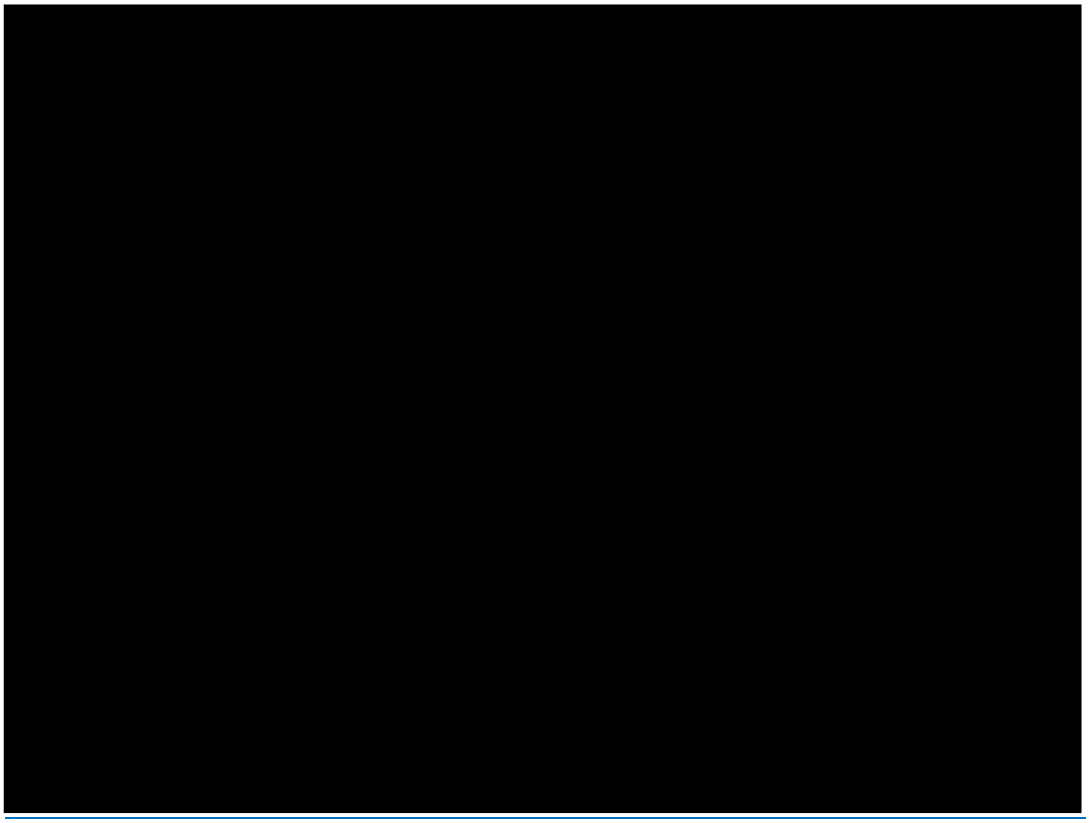


Figure 29: Model OS predictions overlaying CheckMate-142 trial observed OS



B16. Please add a scenario that uses trial weighting for chemotherapy rather than ad-board opinion used for the proportion of patients receiving regimens in Table 82.

Response

Table 28 shows the chemotherapy split in CM8HW, which has been reweighted to exclude bevacizumab, as this is not recommended for use by NICE (2012; TA242). This has been applied within the economic model as outlined in **Table 29**.

Table 28: Chemotherapy regimen split in CM8HW trial and after exclusion of bevacizumab regimens.

	mFOLFOX6	FOLFIRI	mFOLFOX6 + cetuximab	FOLFIRI + cetuximab	mFOLFOX6 + bevacizumab	mFOLFIRI + bevacizumab
CM8HW	10.2%	13.6%	5.7%	6.8%	42.0%	21.6%
Reweighted	28.10%	37.47%	15.70%	18.73%	-	-

This adjusted split increased the cost of chemotherapy from £[redacted] Q2W in the base case to £[redacted]. This increase is mainly due to the increased use of cetuximab-based regimens.

When using the chemotherapy regimens and the splits from above, NIVO + IPI treatment results in QALY gains relative to comparators at a lower cost, thus being dominant **Table 28**.

Table 29: Summary of results when chemotherapy split from CM8HW is used (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	£[redacted]	£[redacted]	£[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI		[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)		[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	Dominant

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B17. PRIORITY QUESTION. Please provide the duration of subsequent treatments in CM-214 by arm and type of subsequent treatment received.

Response

In CM142 the case report form collected subsequent treatment start date but not end date. Therefore, we are unable to report duration of subsequent treatment.

In cohort 3 subsequent cancer therapy was received by 11 (24.4%) of patients, which included radiotherapy for [redacted]%) patient, surgery for [redacted]%) patients, and systemic anti-cancer therapy for [redacted]%) patients (**Table *30***). The most common subsequent systemic therapies were fluorouracil or capecitabine regimen (5FU) for [redacted]%) patients and vascular endothelial growth factor (VEGF) inhibitors for [redacted]%) patients.

Table 30: Subsequent cancer therapy for all treated patients in cohort 3

	Number of Subjects (%)
	n = 45
Any subsequent therapy	[redacted]
Radiotherapy	[redacted]
Yes	[redacted]
No	
Surgery	
Yes	[redacted]
No	[redacted]
Systemic therapy	[redacted]
Oxaliplatin	[redacted]
Irinotecan	[redacted]
5FU (Fluorouracil, Capecitabine)	[redacted]
VEGF-inhibitors (Bevacizumab, Aflibercept, Ramucirumab)	[redacted]
EGFR inhibitors (Cetuximab, panitumumab)	[redacted]
Regorafenib	[redacted]
TAS-102 (TAS-102, Tipiracil/Trifluridine)	[redacted]
Immunotherapy	[redacted]
Nivolumab	[redacted]
Other – experimental drugs	[redacted]
Other - chemotherapy	[redacted]
Cisplatin	[redacted]
Mitomycin	[redacted]
Unassigned	[redacted]
Leucovorin	[redacted]

Patients may have received more than one type of subsequent therapy.

B18. Please include drug wastage in the model using European patient weights or weight data for the UK general population if trial data is not available / the sample size is too small. Please use method of moments to accurately account for wastage.

Response

The mean patient age in the CM8HW trial was 60.9 years old. Therefore, the mean weight, standard error and sample size for women and men in the age group 55-64 reported in the Health Survey for England 2021 were used in this scenario to better reflect the mean weight of patients in England and the impact on drug costs (NHS Digital, 2022). Previous studies have demonstrated that the general population may have indistinguishable characteristics to patients with several conditions (including multiple cancers) (Hatswell et al., 2016). In order to capture the effect of variable weights, a log-normal distribution has been fitted, separately for men and women and 100,000 patients' weights (53,795 women and 46,205 men samples representing the gender split in the CM8HW) have been sampled. A log-normal distribution has been shown in previous work to be the best fit to the distribution of patients characteristics (weight) (Hatswell et al., 2016). The data used to derive the standard deviation (SD) and the resulted scaled mean and scaled SD are shown below (**Table 31**).

Table 31: Summary of parameters used to sample from log-normal distribution

Patients	Mean	SE	SD*	Sample size	Scaled mean**	Scaled SD**
Male	87.73	0.75	16.79	495	4.46	0.19
Female	74.18	0.79	18.74	557	4.28	0.25

Abbreviations: SD, standard deviation; SE, standard error;
SD calculated as: SE√Sample size
**Scaled mean: ln (mean^2 / √ (mean^2 + SD^2))
**Scaled SD: √ (ln((mean^2 + SD^2) / mean^2))

Dosage of ipilimumab- and panitumumab-based regimens is dependent on patients' weight. As such, the 100,000 samples weights were divided by 50 ml (vial dose), to determine the number of ipilimumab vials needed, then multiplied by the cost of a vial and averaged across the cohort, resulting in a cost of [redacted] per administration. This is slightly higher than the cost used in the base case ([redacted]).

Panitumumab is administered with a dosage of 6mg/kg body weight, therefore the sampled weights were multiplied by 6, then divided by the vial dose and multiplied by the cost of vial, and averaged across the cohort, resulting in a cost of £2,022. This is slightly higher than the base case costs of £1,896, thus increasing the costs of chemotherapy.

The impact of these changes on the cost-effectiveness results is illustrated in **Table *32***. NIVO + IPI dominates PEMBRO regimen, and is cost-effective against chemotherapy, with an ICER below the WTP threshold.

Table 32: Scenario analysis: alternative patient weights (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	£282

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B19. PRIORITY QUESTION. Please provide a scenario that includes subsequent therapy for patients who initially received NIVO+IPI, PEMBRO and chemotherapy, based on data from clinical trials.

Response

CM8HW and CM142 only track specific subsequent treatments received, as opposed to treatment regimens. **Table 33** provides available evidence on which treatments have been prescribed as a subsequent treatment within CM8HW.

Table 33: CM8HW subsequent therapies

Subsequent systemic therapy, n (%)	NIVO + IPI (n = 202)	Chemo (n = 101)
Any systemic therapy	[redacted]	[redacted]
On study crossover to NIVO + IPI	[redacted]	[redacted]
Non study systemic therapy	[redacted]	[redacted]
Anti-CTLA4	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]

Anti-PD-1 or anti-PD-L1	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Camrelizumab	[redacted]	[redacted]
Tislelizumab	[redacted]	[redacted]
EGFR inhibitors	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]
Platinum compounds	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]
VEGFR targeted therapy	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Aflibercept	[redacted]	[redacted]
Other systemic therapies	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Irinotecan hydrochloride	[redacted]	[redacted]
Raltitrexed	[redacted]	[redacted]
Trifluridine/tipiracil	[redacted]	[redacted]
MEK, NRAS and BRAF inhibitor	[redacted]	[redacted]
Encorafenib	[redacted]	[redacted]

Patients may have received more than 1 type of subsequent therapy

Subsequent treatments are reported within TA709 for KEYNOTE-177 (**Table 34**). However, these included several regimens that are not available within UK clinical practice in the treatment experienced mCRC setting, including cetuximab and bevacizumab. As a result, TA709 applied subsequent treatment distribution based on clinical opinion.

Table 34: Subsequent treatment distributions as per KEYNOTE-177 (adapted from TA709 company submission Table 57)

Subsequent treatments, %	Pembrolizumab	Standard of care
No treatment	46.3	16.8
FOLFOX	13.2	6.9
FOLFIRI	10	8.2
Cetuximab + FOLFOX	1.6	0
Cetuximab + FOLFIRI	1.3	0
Bevacizumab + FOLFOX	15.6	30.9
Bevacizumab + FOLFIRI	11.9	37.1

FOLFIRI: fluorouracil, folinic acid and irinotecan; FOLFOX: fluorouracil, folinic acid and oxaliplatin

In order to address this request, data from KEYNOTE-177 and CM8HW were used to develop a subsequent treatment distribution based on clinical trials but relevant to clinical practice. Subsequent treatment in the NIVO+IPI and PEMBRO arms was based on the PEMBRO arm of KEYNOTE-177, reweighted to exclude bevacizumab and cetuximab. Immunotherapy as a subsequent therapy in the modelled chemotherapy arm was based on usage in the chemotherapy arm of the CM8HW study (NIVO+IPI: [redacted]/101 patients, [redacted] patients as crossover and [redacted] patients outside of study protocol; PEMBRO: [redacted]/101 patients). The remaining patients are assumed to receive chemotherapy, reweighted based on subsequent treatments in the chemotherapy arm of KEYNOTE-177 (excluding bevacizumab and cetuximab).

Table 35: Subsequent treatments applied in scenario

Subsequent treatments	Modelled treatment arm		
	NIVO+IPI	PEMBRO	Chemotherapy
FOLFOX	56.90%*	56.90%*	[redacted]
FOLFIRI	43.10%*	43.10%*	[redacted]
NIVO+IPI	-	-	[redacted]
PEMBRO	-	-	[redacted]

* Informed by PEMBRO arm of KEYNOTE-177, reweighted to exclude bevacizumab and cetuximab

† Informed by immunotherapy use in CM8HW.

‡ Remaining patients receive chemotherapy aligned with chemotherapy arm of KEYNOTE-177 (excluding bevacizumab and cetuximab)

These subsequent treatment distributions were applied in two scenarios: one applied post-progression survival in the chemotherapy arm aligned with submission base case analysis, while the other used post-progression survival as in question B21a.

Table 36 provides outcomes for the scenario assuming post-progression survival as in the submission base case analysis. There is a slight decrease in subsequent treatment costs in the NIVO + IPI and PEMBRO arms, with limited impact on total costs. By contrast, there is a larger decrease in subsequent treatment costs in the chemotherapy arm, resulting in total costs decreasing from [redacted] to [redacted]. However, the resulting ICER remains cost-effective for NIVO + IPI.

Table 36: Scenario analysis - Trial-based subsequent treatment with post-progression survival in chemotherapy arm aligned with submission base case analysis

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	£3,950

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 37 provides outcomes using OS data from CM142 cohort 2 (2L+ NIVO + IPI) to inform the chemotherapy arm post-progression survival. Given that NIVO + IPI use is reduced to less than 50% in this scenario, use of this survival lacks face validity. However, the outcomes are provided for completeness. Subsequent treatment costs in the chemotherapy arm are increased against the base case analysis due to longer time on treatment, as more patients remain alive for longer in the progressed disease state. Subsequent treatment costs are also slightly increased versus those in the Question B21a scenario (**Table *54***), due to inclusion of pembrolizumab. As a result, NIVO + IPI is dominant versus chemotherapy in this scenario.

Table 37: Scenario analysis - Trial-based subsequent treatment with post-progression survival in chemotherapy arm aligned with B21a

	NIVO + IPI	Chemotherapy
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B20. Please justify not presenting cost-effectiveness analysis according to mutation status given the chemotherapy comparator differs.

Response

In the CM8HW subgroup analysis, the HR for progression in the KRAS-mutation (subgroup n=45) was similar to the HR (95% CI) for the whole centrally-confirmed population 0.24 [0.09, 0.63] vs. 0.20 [0.14, 0.31]). KRAS mutation appear to have no significant impact on the comparative efficacy of NIVO + IPI. Additionally in the base case the use of the different types of chemotherapy regimens/mutation status are weighted according to the proportion of patients receiving each regimen in the experience of UK clinical experts attending a BMS UK advisory board (see table 82).

Table 82 (of Document B): Total weighted chemotherapy costs per model cycle

Regimen	Advisory board opinion	Proportion weighting
FOLFOX	87.5%	29.17%
FOLFIRI		29.17%
CAPOX		29.17%
Capecitabine	0%	0% (assessed in scenario)
FOLFOXIRI	5%	5%
FOLFOX + cetuximab	7.5%	1.875%
FOLFIRI + cetuximab		1.875%
FOLFOX + panitumumab		1.875%
FOLFIRI + panitumumab		1.875%

Below we present the cost-effectiveness for adults when 100% of chemotherapy patients are allocated to the relevant chemotherapy regimen in **Table *38*** to **Table *53***. The result show that in all cases; RAS mutation, EGFR expressing RAS wild type mutation, non-EGFR expressing mutation and other non-mutation specific treatments, NIVO + IPI is very cost-effective compared to chemotherapy with and without PAS (PAS = Dominant to £2,558 per QALY, without PAS = [redacted] to [redacted] per QALY).

The following analyses assumes no change in efficacy as in the CM8HW subgroup analysis, the HR for progression in the KRAS-mutant subgroup was similar to the HR for the whole population. Chemotherapy drug acquisition costs will be assumed to be 100% usage of the regimen allocated to each mutation type in sections A to Fiii.

A. Chemotherapy is 100% FOLFOXIRI for the RAS mutation

Table 38: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 39: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

B. Cetuximab with FOLFOX for EGFR expressing RAS wild type mutation

Table 40: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 41: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYG: life years gained; LYs: life years; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

C. Cetuximab FOLFIRI for EGFR expressing RAS wild type mutation

Table 42: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 43: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

D. Panitumumab with FOLFOX for RAS wild type EGFR expressing and non-EGFR expressing mutations

Table 44: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 45: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

E. Panitumumab FOLFIRI for RAS wild type EGFR expressing and non-EGFR expressing mutations

Table 46: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 47: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

F. Other chemotherapy treatments in the standard of care arm (no mutation).

i. MFOLFOX6

Table 48: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 49: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

ii. FOLFIRI

Table 50: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 51: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

iii. CAPOX

Table 52: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 53: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

B21. PRIORITY QUESTION: It does not appear reasonable to assume equal PPS for all arms given that different options are available for subsequent treatment (e.g. nivo+ipi is available after chemotherapy and not after nivo+ipi).

a) Please provide an analysis using data from your later line trial to inform subsequent treatment as an alternative analysis or to replace the base case post chemotherapy.

Response

OS data from CM142 cohort 2 (2L+ NIVO + IPI) was used to derive an exponential log rate ([redacted]) to inform a scenario analysis. As patients in the chemotherapy arm would be living for a long period in the progressed disease state, BSC costs were no longer appropriate to apply for the entirety of that time. As a result, BSC costs were removed from the analysis in order to provide an unbiased scenario.

Outcomes from this analysis are provided in **Table *54***; disaggregated results are provided in **Table *55*** to ensure transparency and support face validity.

Use of CM142 OS increased LY accrual in the progressed disease state to [redacted], resulting in a total of [redacted] LYs. This is slightly below the total LYs reported for the second-line NIVO + IPI arm in the company submission for TA716 ([redacted] Lys) (NICE, 2021b) but retains face validity when viewed within a treatment pathway using first-line chemotherapy. QALY accrual was also increased in the progressed disease state,

increasing from [redacted] to [redacted], which is comparable with total QALYs from the company submission in TA716 ([redacted]) (NICE, 2021b).

Longer use of second-line NIVO + IPI in the chemotherapy arm also increased total costs of subsequent treatment, from [redacted] in the base case to [redacted] in the scenario. This reflects longer time on treatment, as more patients remain alive for longer in the progressed disease state.

As a result of these changes, NIVO + IPI is dominant versus chemotherapy in this scenario.

Table 54: Scenario analysis: CM142 cohort 2 OS as PD-D transition (with PAS)

	NIVO + IPI	Chemotherapy
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 55: Scenario analysis: CM142 cohort 2 OS as PD-D transition (with PAS) - disaggregated outcomes

	NIVO + IPI	Chemotherapy
Clinical outcomes		
QALYs (discounted)	[redacted]	[redacted]
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Disutility of grade 3-4 AE	[redacted]	[redacted]
Life years (undiscounted)	[redacted]	[redacted]
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Cost outcomes (discounted)		
Total Costs	[redacted]	[redacted]
Treatment-related costs	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]
Total resource use	[redacted]	[redacted]
Resource use	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]

Bold italicised values are updated from base case analysis.

BSC costs removed from analysis to ensure face validity.

b) Please comment on the applicability of data from CM-142 to pembrolizumab based on how similar (or not) the subsequent treatments received in CM-142 are to those in KN-177 and how similar the treatments expected to be received in practice after these two therapies are.

Response

BMS do not have access to details about the subsequent therapy in KN177, however it has been published (Helwick, 2021) that 28.8% of patients in the pembro arm received subsequent therapy, primarily with oxaliplatin-based regimens. In NICE TA709 clinical experts explained that the KN177 trial included

cetuximab as a subsequent therapy. 7 patients received pembrolizumab again, some as per protocol for disease relapse after completion of 2 years of first-line pembrolizumab.

In cohort 3 of CM142, six patients received subsequent systemic therapy. The most common subsequent systemic therapies were 5FU regimens in 8.9% of patients (n=4). Oxaliplatin, cisplatin or irinotecan were used in 6.7% of patients (n=3). VEGF inhibitors (bevacizumab, aflibercept, ramucirumab) were used in 6.7% patients (n=3). Only 1 patient received nivolumab as a subsequent therapy in CM142 compared to 7 patients receiving an immuno-oncology treatment in KN177.

The limited detail available for KN177, and small numbers of subsequent systemic therapies in CM142 limit conclusions around similarity between the trials or to UK clinical practice. The two trials were similar in their subsequent therapy in that chemotherapy was the most common subsequent systemic therapy. This would also reflect clinical practice in the UK. The use of 2L VEGF, eGFR and immunotherapy agents after 1L immunotherapy in both trials does not reflect UK practice, as these are not approved in this setting according to NICE TA242.

c) **We heard from a clinical expert that around 50% of patients get pembrolizumab rather than nivolumab + ipilimumab as subsequent treatment post chemotherapy as they are unsuitable for treatment with the doublet. Please provide a scenario analysis assuming this allowing for the difference in effectiveness between the two treatments or provide alternate data on what proportion get each option 2nd line.**

Response

In this scenario analysis patients that received first line treatment with chemotherapy are assumed to receive second line treatment with NIVO + IPI or pembro (50% receiving each immune-oncology option). Outcomes from this analysis are provided in **Table *56***; disaggregated results are provided in **Table *57*** to ensure transparency and support face validity. Use of pembrolizumab increased total costs of subsequent treatment to [redacted] in this scenario. This reflects the higher cost of pembrolizumab in

the absence of the PAS. NIVO + IPI remains dominant versus chemotherapy in this scenario.

It is unclear if it is plausible to assume that up to 50% of patients are unable to receive NIVO + IPI. As such, a scenario analysis has been conducted to assess the impact of different thresholds of pembrolizumab use (05 to 50%), which has been provided in **Table 58**. In all cases NIVO + IPI remains dominant versus chemotherapy.

Table 56: Scenario analysis: CM142 cohort 2 OS as PD-D transition and pembrolizumab and NIVO + IPI as subsequent therapy (with PAS)

	NIVO + IPI	Chemotherapy
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 57: Scenario analysis: CM142 cohort 2 OS as PD-D transition and pembrolizumab and NIVO + IPI as subsequent therapy (with PAS) - disaggregated outcomes

	NIVO + IPI	Chemotherapy
Clinical outcomes		
QALYs (discounted)	[redacted]	[redacted]
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Disutility of grade 3-4 AE	[redacted]	[redacted]
Life years (undiscounted)	[redacted]	[redacted]
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Cost outcomes (discounted)		
Total Costs	[redacted]	[redacted]
Treatment-related costs	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]
Total resource use	[redacted]	[redacted]
Resource use	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]

Bold italicised values are updated from base case analysis.

BSC costs removed from analysis to ensure face validity.

Table 58: Scenario analysis: CM142 cohort 2 OS as PD-D transition and pembrolizumab and NIVO + IPI as subsequent therapy (with PAS) – pembrolizumab threshold analysis

NIVO + IPI proportion (%)	Pembrolizumab proportion (%)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
50%	50%	[redacted]	[redacted]	Dominant
60%	40%	[redacted]	[redacted]	Dominant
70%	30%	[redacted]	[redacted]	Dominant
80%	20%	[redacted]	[redacted]	Dominant
90%	10%	[redacted]	[redacted]	Dominant
100%	0%	[redacted]	[redacted]	Dominant

Section C: Textual clarification and additional points

C1. PRIORITY QUESTION: Please provide CSRs with all appendices. If the following outcomes are not available in the CSR please provide these separately for all study arms for both trials including nivolumab monotherapy:

Response

Unfortunately the CSRs for CM8HW and CM142 were accidentally omitted from the reference pack submitted to NICE. The CSRs are included in the reference pack submitted with this response.

- **% receiving each dose at each timepoint out of the total population and the total eligible population (those remaining on treatment)**

Response

The percentage of patients receiving each dose at each timepoint are resented below in **Table *59***.

Table 59: Proportion of Subjects on Therapy - All Nivolumab + Ipilimumab Treated Subjects

Trial	CM8HW				CM142	
Denominator	Total number of subjects treated	Kaplan Meier Estimates	Total number of subjects treated	Kaplan Meier Estimates	Total number of subjects treated	Kaplan Meier Estimates
Months	Proportion of subjects still receiving treatment, at risk of discontinuing treatment (%)					
	Arm B	Arm B	Arm C	Arm C	Cohort 3	Cohort 3
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12						
18						
24						
30						
36	-	-				
42	-	-				
48	-	-	-	-		
54	-	-	-	-		

- **Time to next treatment (including Kaplan Meier)**

Response

The Kaplan Meir curves for time to next treatment are presented below in **Figure 30** to **Figure 32**.

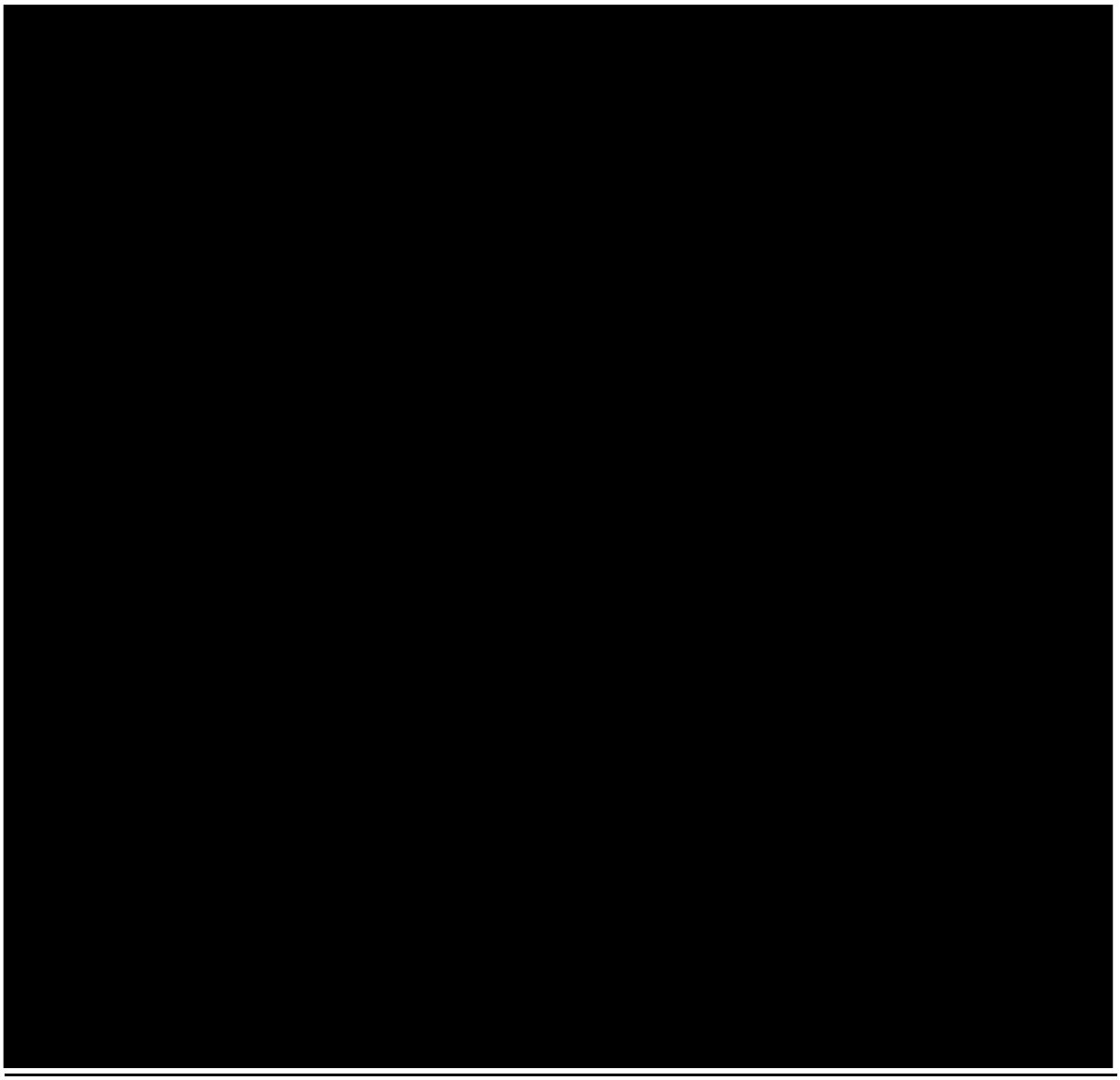
Figure 30 Kaplan-Meier Plot of Time to Subsequent Treatment - All Nivolumab + Ipilimumab Treated Subjects (Arm B CM8HW)

Symbols represent censored observations.

Figure 31: Kaplan-Meier Plot of Time to Subsequent Treatment - All Chemotherapy Treated Subjects (Arm C CM8HW)

Symbols represent censored observations.

Figure 32: Kaplan-Meier Plot of Time to Subsequent Treatment - All 1L Nivolumab + Ipilimumab Treated Subjects (CM142)



Symbols represent censored observations.

- **PFS2 (including Kaplan Meier)**

Response

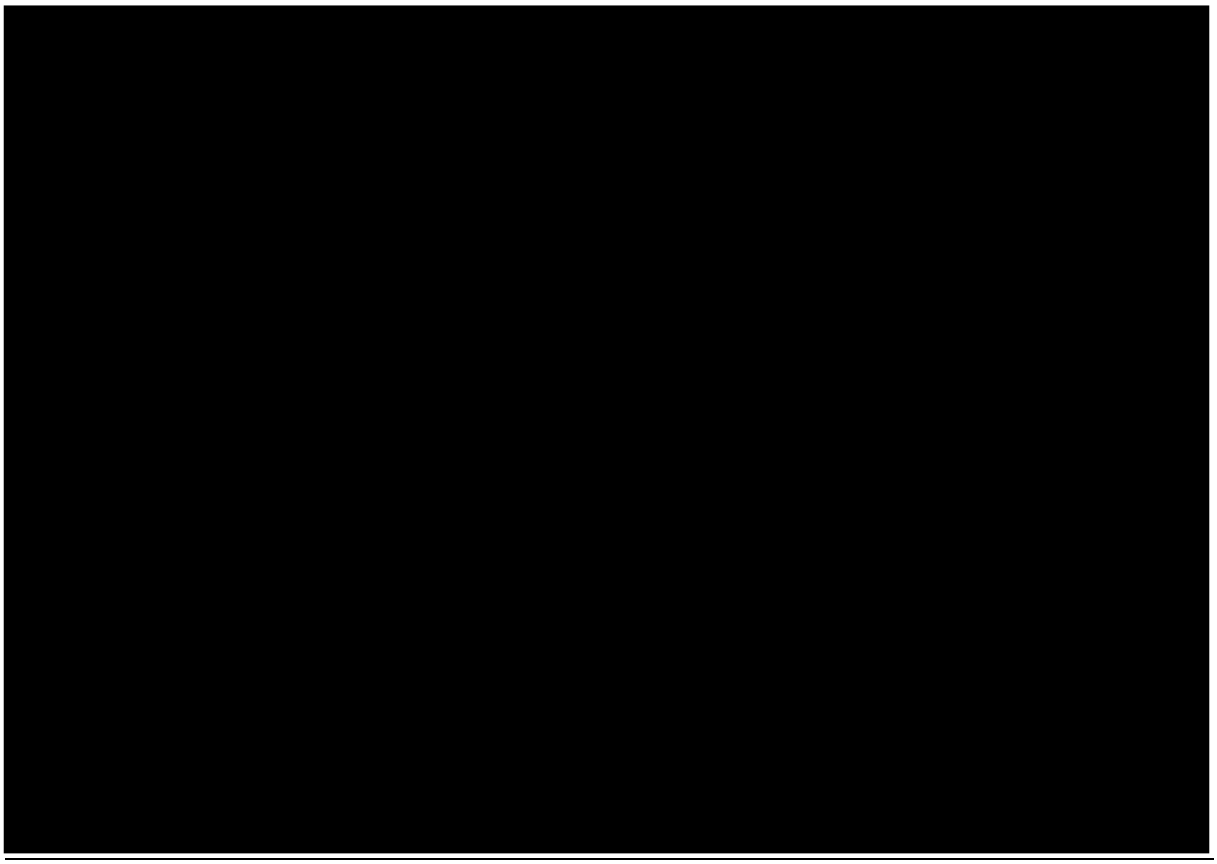
Data on PFS2, time from randomisation to objective tumour progression on next-line treatment or death from any cause, was not captured in the CM142 study. **Table *60*** and **Figure 33** summarises the PFS 2 data for CM8HW.

Table 60: Summary of Efficacy for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC

Exploratory Endpoints PFS2 (per Investigator)	Arm B: Nivo+Ipi (n=171)	Arm C: Chemo (n = 84)
Events, n (%)		
Median PFS2 (95% CI), mo.[a]		
HR (95% CI)[b]		
PFS2 Rates (95% CI), % [a]		
6-month		
Number of Subjects at Risk		
12-month		
Number of Subjects at Risk		

a = Based on Kaplan-Meier estimates; b = HR from a Cox proportional hazard model stratified by tumour sidedness (left vs right) per IRT.

Figure 33: Progression-Free Survival on Next Line of Therapy (PFS2) for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC



- **List of subsequent treatments**

Response

Subsequent cancer therapies for CM8HW and CM142 are presented respectively in **Table 61** and **Table 62**.

Table 61: Subsequent Cancer Therapy: All 1L Randomized Subjects in the Nivo+Ipi and Chemo Arms (CM8HW)

	Number of Subjects (%)		
	Arm B: Nivo + Ipi (n = 202)	Arm C: Chemo (n = 101)	Total (n = 303)
Subjects with any subsequent therapy (%) (1) (2)	[redacted]	[redacted]	[redacted]
Subjects who received subsequent radiotherapy (%)	[redacted]	[redacted]	[redacted]
Subjects who received subsequent surgery (%)	[redacted]	[redacted]	[redacted]
Subjects who received subsequent systemic therapy (%) (2)	[redacted]	[redacted]	[redacted]
Crossover treatment	[redacted]	[redacted]	[redacted]
Non-study systemic therapy	[redacted]	[redacted]	[redacted]
Anti-CTLA4	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]
Anti-PD1 or anti-PDL1	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]
Camrelizumab	[redacted]	[redacted]	[redacted]
Tiselizumab	[redacted]	[redacted]	[redacted]
EGFR inhibitors	[redacted]	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]	[redacted]
Platinum compounds	[redacted]	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]	[redacted]
VEGFR targeted therapy	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Aflibercept	[redacted]	[redacted]	[redacted]
Other systemic anticancer therapies	[redacted]	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]
Irinotecan hydrochloride	[redacted]	[redacted]	[redacted]
Raltitrexed	[redacted]	[redacted]	[redacted]
Tipiracil hydrochloride; Trifluridine	[redacted]	[redacted]	[redacted]
Tipiracil; Trifluridine	[redacted]	[redacted]	[redacted]
MEK NRAS and BRAF inhibitors	[redacted]	[redacted]	[redacted]
Encorfenib	[redacted]	[redacted]	[redacted]

Clinical Data Cutoff Date: 12-Oct-2023.
Excludes surgery, radiotherapy, or non-study systemic therapy data collected on or after first crossover dose date.
(1) Subject may have received more than 1 type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).
(2) Subjects who received Crossover treatment in Arm C are counted.

Table 62: Subsequent Cancer Therapy Summary - All Treated Cohort 3 Subjects (CM142).

	Number of Subjects (%)
	All Subjects (n = 45)
Subjects with any subsequent therapy (%)	[redacted]
Radiotherapy (%)	
Yes	[redacted]
No	[redacted]
Surgery (%)	
Yes	[redacted]
No	[redacted]
Systemic therapy (%)	[redacted]
Oxaliplatin	[redacted]
Irinotecan	[redacted]
5FU (fluorouracil, capecitabine)	[redacted]
VEGF-inhibitors (bevacizumab, aflibercept, ramucirumab)	[redacted]
EGFR inhibitor (cetuximab, panitumumab)	[redacted]
Regorafenib	[redacted]
Tas-102 (Tas-102, tipiracil/trifluridine)	[redacted]
Immunotherapy	[redacted]
Nivolumab	[redacted]
Other – experimental drugs	[redacted]
Other - chemotherapy	[redacted]
Cisplatin	[redacted]
Mitomycin	[redacted]
Unassigned	[redacted]
Leucovorin	[redacted]

Subject may have received more than one type of subsequent therapy

- **Response (in particular proportion with best response of CR, PR, SD and PD)**

Response

In accordance with the interim CSR for CM8HW, the other primary endpoint (PFS per BICR for nivo+ipi versus nivo monotherapy in all randomized subjects) was not tested due to not reaching the required number of PFS events to trigger its interim analysis. Because this primary endpoint was not tested, none of the secondary endpoints included in the hierarchical testing strategy were tested at this interim analysis and these endpoints remained blinded.

Table *63* below summarizes the efficacy results for treated subjects in Cohort 3 of CM142.

Table 63: Summary of Efficacy Results - All Treated Cohort 3 Subjects in CM142

Efficacy Parameter	Investigator-assessed (n = 45)	BICR-assessed (n= 45)
ORR[a] , n (%)		
95% CI		
DCR[b] **, n (%)**		
95% CI		
BOR[c]		
CR, n (%)		
(95% CI)		
PR, n (%)		
(95% CI)		
SD, n (%)		
PD, n (%)		
Unable to Determine, n (%)		
TTR		
Number of Responders		
Median, months		
Range		
DOR		
# Events / # Responders (%)		
Median[d] (95% CI), Months		
Range[e]		
24-month DOR Rate (95% CI)		
Subjects with DOR:		
≥ 6 months, n (%)		
≥ 12 months, n (%)		
Subjects with Ongoing Response, n (%)[f]		
PFS		
Number of Events, n (%)		
Median[d] PFS (95% CI), Months		
6-month rate (95% CI)		
12-month rate (95% CI)		
24-month rate (95% CI)		
36-month rate (95% CI)		
OS		
Number of Events (%)		
Median[d] OS (95% CI), Months		
6-month rate (95% CI)		
12-month rate (95% CI)		
24-month rate (95% CI)		

36-month rate (95% CI)		[redacted]

a = complete response +PR.
b = complete response + partial response + stable diseaes (for at least 12 weeks).
c = Per RECIST 1.1 criteria.
d = Median computed using Kaplan-Meier method.
e = Symbol + indicates a censored value.
f = Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis and excludes responders censored prior to 8 weeks of the clinical data cutoff date if a patient is still in the first 24 weeks follow-up period, otherwise, the window is 14 weeks.

- **Kaplan Meier data for mutation subgroups for PFS**

Response

Please see **Figure *34*** and **Figure *35***.

Figure 34: Kaplan-Meier Plot of Progression-free Survival per BICR by KRAS/BRAF Mutation Status - All Treated Subjects

Figure 35: Progression-Free Survival per BICR (Primary Definition) in Pre-Defined Subsets for Nivo+Ipi vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC

C2. The footnote for the dagger symbol in Figure 11 is missing. Please provide this.

Response

The footnote was intended to caveat the treatment discontinuation rules listed in the diagram as follows: 'treatment beyond initial evidence of progressed disease was permitted if the patient tolerated the study drug and benefited from study treatment per investigator assessment'. Further detailed requirements for treatment continuation beyond investigator assessed disease progression are listed in Table 21 of Document B.

C3. Please provide the KM plots for the data presented in Table 31.

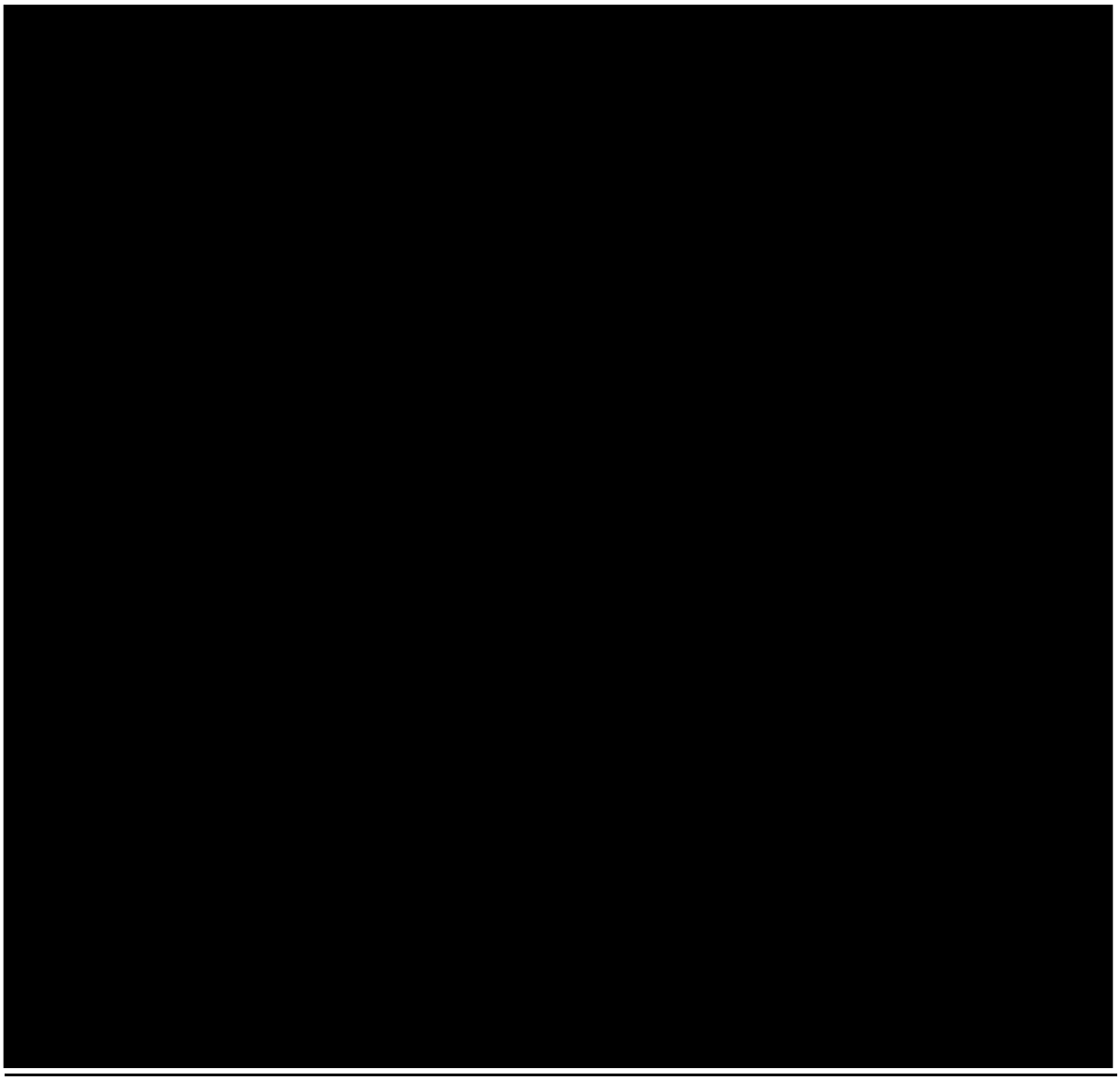
Response

Below are the KM curves (**Figure 36** to **Figure 38**) for the information provided in Table 31 of Document B.

Figure 36: Kaplan-Meier Plot of Progression Free Survival per Primary Definition per BICR - All Randomized Subjects - Arm C (Bevacizumab cohort)

Symbols represent censored observations.

Figure 37: Kaplan-Meier Plot of Progression Free Survival per Primary Definition per BICR - All Randomized Subjects - Arm C (Cetuximab cohort)



Symbols represent censored observations.

Figure 38: Kaplan-Meier Plot of Progression Free Survival per Primary Definition per BICR - All Randomized Subjects - Arm C (No Bevacizumab or Cetuximab)

Symbols represent censored observations.

C4. PCR is not defined in a number of tables, please provide a definition.

Response

PCR stands for 'polymerase chain reaction' in the submission documents.

C5. Please provide definition of "NR" (Table 7 appendix N1) – is it 'not reported', 'not reached' or something else?

Response

NR is defined as ‘not reported’. In this table this refers to baseline characteristics which were not available from the published evidence for KEYNOTE-177 and PRIME studies.

C6. Please provide unredacted data from TA716 in Table 49 given that this is a submission conducted by yourselves.

Response

Please see the below excerpt from Table 49 (Document B) which is updated to include unredacted TA716 data. Please note this data should still be considered commercial in confidence.

Table 49 (Document B): Summary list of published cost-effectiveness studies

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
NICE TA716 [Nivolumab + ipilimumab], 2021	Nivolumab + ipilimumab (Company's base-case results with PAS)	GBP (2018-19)	[redacted]	Undiscounted: [redacted]	NR	[redacted]	NR	Reference	The model evaluates nivolumab + ipilimumab as third-line treatment. The analysis is conducted from NHS Healthcare payer perspective using a partitioned survival model for Lifetime (up to 50 years or 2,609 weeks) horizon with 3.5% discount rate. Scenario analysis, PSA And DSA was performed.
	Trifluridine/ tipiracil (Company's base-case results with PAS)		16,978	Undiscounted: 0.915	NR	0.63	NR	13,367	
	BSC (Company's base-case results with PAS)		9,379	Undiscounted: 0.639	NR	0.441	NR	14,211	
	FOLFIRI (Company's base-case results with PAS)		12,176	Undiscounted: 1.314	NR	0.884	NR	14,839	
	FOLFOX (Company's base-case results with PAS)		11,527	Undiscounted: 1.284	NR	0.874	NR	14,930	
	Irinotecan (Company's base-case results with PAS)		11,139	Undiscounted: 1.295	NR	0.883	NR	15,022	
	Raltitrexed (Company's base-case results with PAS)		13,389	Undiscounted: 1.71	NR	1.147	NR	15,346	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	BSC (ERG's base case results)		9,303	NR	NR	0.376	NR	Reference	
	FOLFIRI (ERG's base case results)		11,525	NR	NR	0.822	NR	4,982	
	FOLFOX (ERG's base case results)		12,334	NR	NR	0.877	NR	14,709	
	Nivolumab + ipilimumab (ERG's base case results)		[redacted]	NR	NR	[redacted]	NR	40,976	
	Nivolumab + ipilimumab (Company's revised base case results)		[redacted]	[redacted]	NR	[redacted]	NR	Reference	
	Trifluridine/ tipiracil (Company's revised base case results)		17,020	0.967	NR	0.689	NR	15,743	
	BSC (Company's revised base case results)		9,546	0.691	NR	0.477	NR	16,323	
	FOLFOX (Company's revised base case results)		12,564	1.546	NR	1.029	NR	17,220	

Study ID Country	Treatment (Intervention Comparator)	Currency (year)	Total costs	Total life-years	Life-year gain	Total QALYs	ICER (base case) Incremental cost/life-year gain	ICER (base case) Incremental cost/QALY gain	Summary of Model
	FOLFIRI (Company's revised base case results)		12,289	1.931	NR	1.287	NR	17,981	

D1. What is the reason the model looks at PrePS independently rather than predicting PFS and calculating PrePS as PFS - TTP as is done in TA709?

Response

Due to data immaturity, OS and other secondary endpoints were not tested in the interim CM8HW analysis, as per the hierarchical testing strategy pre-defined in the trial protocol. As such, it was not permissible to assess mortality data from the CM8HW within the economic analysis. As CM8HW mortality is not available, independent sources were required. General population mortality was used to inform pre-progression mortality within the base case analysis. This approach was validated during a global advisory board, which included economists and clinical experts, as well as a UK-specific advisory board, where it was considered appropriate.

Further, the model outputs validate well against CM8HW PFS data for the NIVO + IPI, as shown in

Table 64, the economic model increased PFS in the chemotherapy arm, this will lead to cost-effectiveness outcomes favouring chemotherapy, meaning that the ICERs for NIVO+ could be considered conservative.

Table 64:Comparison of CM8HW PFS and economic model progression free state occupancy

	NIVO + IPI		CHEMO	
	CM8HW PFS[1]	Economic model progression free occupancy	CM8HW PFS[1]	Economic model progression free occupancy
One year	71.15%	[redacted]	23.70%	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]

Additionally, a scenario analysis was conducted where data from CheckMate 142 was used to inform this input (Company submission, Document B Section B.3.9.3.1.2). **Table 65** shows a comparison between this scenario analysis and the base case analysis, demonstrating that applying general population mortality may be considered the more conservative approach compared with using CheckMate 142 inputs.

Table 65: Submission base case analysis compared with scenario analysis applying CM142 for PF-D transition (with PAS)

	Base case analysis			Scenario analysis		
	NIVO + IPI	PEMBRO	Chemo	NIVO + IPI	PEMBRO	Chemo
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant	£332	-	Dominant	Dominant

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab plus ipilimumab for untreated metastatic colorectal cancer with high microsatellite instability or deficient mismatch repair [ID1136]

Clarification questions Addendum

August 2024

File name	Version	Contains confidential information	Date
	V2	Yes	23rd August 2024

Section B: Clarification on cost-effectiveness data

B7. PRIORITY QUESTION. A generalized gamma model was chosen for the extrapolation of TTP based solely on its low AIC value. Additionally, the visual fit to the nivo+ipi arm is poor. Please present an assessment of the clinical plausibility and long-term data to support this choice and consider whether a more complex model is required to better fit the nivo+ipi arm.

Response

The decision to use a generalised gamma model is detailed extensively in the Company Submission Document B Section B.3.3.1.1 (page 170-171) and in Appendix O Section 3.2.2 (page 31-32). While AIC is considered, others factors assessed are aligned with NICE DSU TSD 14 (NICE, 2011) and include visual inspection of fit to data, log cumulative hazard plots and plausibility of long-term extrapolations. Additionally, external data was used to validate selections, as detailed in Company Submission Document B Section B.3.13.1.1 (page 273-275) and in Appendix O Section 4.1 (page 64-66). As evidence of the decision process, generalised gamma was selected as most appropriate in the chemotherapy arm, despite a slightly higher AIC compared with lognormal ([redacted] compared with [redacted]). As such, it is incorrect to say that "a generalized gamma model was chosen for the extrapolation of TTP based solely on its low AIC value".

a) Rationale for survival modelling approach

The survival analysis presented in the company submission is aligned with NICE DSU TSD 14 and 21 (NICE, 2011, 2020). In line with this approach, the following activities were undertaken sequentially:

- Log-cumulative hazard and quantile-quantile plots were assessed.
- As the plots were not parallel, individual models were fitted.
- Standard parametric fits were assessed for suitability.

- Generalised gamma was considered most appropriate as it is a flexible model and able to fit the changing hazard profile, as reflected by goodness of fit statistics (AIC/BIC) and visual assessment of fit to observed data.

More complex approaches, such as spline models and piecewise approaches, are used where standard parametric fits are inappropriate to reflect the data. (NICE, 2011, 2020). While complex flexible models are able to fit observed data well, these models reduce to standard Weibull, lognormal or log-logistic models beyond the trial period (Latimer and Adler, 2022). Depending on where knots are placed within a spline, this may limit data available to inform the extrapolation phase and reduce face validity. As such, a complex model might be preferred if the hazard function is continuously varying, rather than one in which the early data are progressively less influential over time, as with a spline.

It is acknowledged that other standard parametric fits were less able to capture the changing hazard profile, with a resulting impact on visual fit to observed data and goodness of fit statistics. By contrast, the generalised gamma had the lowest AIC ([redacted]) by a large margin (log logistic [redacted], log normal [redacted]). Additionally, the generalised gamma was also the only model that reflected the increased hazards between month 0 and month 6 in the observed NIVO + IPI arm, as well as the reduced hazards over time. Log-logistic and lognormal fits were also considered potentially plausible, but the fits were not considered as appropriate as generalised gamma, based on observed fit to the data and goodness of fit data.

In addition to being the best fit in terms of AIC and visual assessment of fit to observed data in the NIVO + IPI arm, the generalised gamma fit was also chosen for the chemotherapy arm. Similarly, as part of the ITC, generalised gamma was the best fit for pembrolizumab, based on digitised KEYNOTE-177 Kaplan-Meier data. Based on guidance from NICE DSU TSD 14 (NICE 2011), “when parametric models are fitted separately to individual treatment arms it is sensible to use the same ‘type’ of model”. Therefore, using the generalised gamma for NIVO + IPI follows this best practice guidance.

b) Assessment of clinical plausibility

The parametric survival curves were presented to a UK advisory board and a global advisory board that included clinical experts and health economists, where standard parametric fits were considered plausible, although no specific extrapolation was preferred. However, the experts stressed the importance of external validation.

External validation of survival curves was assessed using data from CheckMate 142 (Company Submission Document B Section B.3.3.1.1.2 Table 57), KEYNOTE-177 and Tougeron et al., (2020) (Company Submission Document B Section B.3.3.1.2.2 Table 60). Validation of these survival curves is reproduced below, adapted to account for EAG request in B8 and B9. Additionally, economic model outcomes were assessed for plausibility using data from CheckMate 142 and KEYNOTE-177 (Company Submission Document B Section B.3.13.1).

The estimates of the median TTP, one-year, two-year, and five-year progression-free probability generated by the extrapolation of the CM8HW NIVO + IPI arm were compared against PFS data from CM142 Cohort 1 (2L+ mCRC receiving NIVO monotherapy), Cohort 2 (2L+ mCRC receiving NIVO + IPI) and Cohort 3 (1L mCRC receiving NIVO + IPI), as described in Table 1. Observed TTP in CM142 cohorts 2 and 3 was comparable with all parameterisations at year 1, but generalised gamma was the best fit at years 2 and 3. This comparison demonstrates that the generalised gamma extrapolation has the most face validity. Lognormal and log-logistic extrapolations can be considered highly conservative but may still be plausible.

The extrapolated TTP estimates for the CM8HW chemotherapy arm were validated against PFS outcomes from the published literature, i.e., Tougeron et al., (2020) and chemotherapy PFS data from KN-177 published by Diaz et al., (2022). TTP and PFS cannot be considered interchangeable, as TTP is defined as time from randomisation to progression with censoring for death events whereas PFS is defined as time from randomisation to progression or death. As such, PFS will be expected to be lower than TTP. However, as mortality is low prior to progression, PFS can be used to assess face validity of TTP estimates. As outlined in Table 60 (Document B), the median estimated TTP for the CM8HW chemotherapy arm is relatively similar to the estimated value in both validation sources and lie within the 95% CIs of both validation estimates. With regards to the estimated landmark survival values, the 95% CI of all 3-year CM8HW extrapolations encompass the estimated 3-year PFS from KN-177 (Diaz et

al., 2022). At 5-years, the generalised gamma extrapolated fit TTP for CM8HW validates the best to KN-177 (Diaz et al., 2022).

Table 1: Comparison of landmark survival values for CM8HW NIVO + IPI TTP extrapolation versus CM142 observed values

		Median, years (95% CI)	1-year progression -free	2-year progression -free	5-year progression -free
CM8HW NIVO + IPI	Observed TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic TTP	[redacted]	[redacted]	[redacted]	[redacted]
CM142[7,8]	Cohort 1 (2L+ NIVO) TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Cohort 2 (2L+ NIVO + IPI) TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Cohort 3 (1L NIVO + IPI) TTP	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IPI, ipilimumab; NE, not evaluable; NIVO, nivolumab; NR, not reached; PFS, progression-free survival; TTP: time to progression.

Table 2: Comparison of landmark survival values for CM8HW chemotherapy TTP extrapolation versus Tougeron et al., (2020) and KN-177

		Median, years (95% CI)	1-year progression-free	3-year progression-free	5-year progression-free
CM8HW chemotherapy	Observed TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Lognormal TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised gamma TTP	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic TTP	[redacted]	[redacted]	[redacted]	[redacted]
Tougeron et al. (2020)	1L chemotherapy PFS	6.0 (5.0, 7.8)	-	-	-
KN-177	1L chemotherapy PFS	8.2 (6.2, 10.3)	-	13%	8%

TTP defined as time from randomisation to progression, censored at subsequent treatment or death events. PFS defined as time from randomisation to progression or death, censored at subsequent treatment. PFS will be expected to be lower than TTP. However, as mortality is low prior to progression, PFS can be used to assess face validity of TTP estimates.

Abbreviations: CI, confidence interval; NR, not reached; PFS, progression-free survival; TTP, time to progression.

c) Alternative survival models

All alternative standard parametric fits were assessed in the economic model as scenario analyses, as outlined in Company Submission Document B Section B.3.9.3.2.2 and Section B.3.9.3.2.3, including extrapolations lacking clinical face validity. These scenarios demonstrate that even implausibly conservative extrapolations did not greatly impact cost-effectiveness conclusions.

Table 3: Scenario analysis: alternative NIVO + IPI TTP extrapolations - adult population (with PAS)

NIVO + IPI TTP extrapolations (ordered by AIC)	PEMBRO			Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
Generalised Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,836
Lognormal	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,780
Log-logistic	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,754
Gompertz*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,779
Weibull	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,855
Gamma	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£1,887
Exponential*	[redacted]	[redacted]	Dominant	[redacted]	[redacted]	£584

*Clinically implausible extrapolations, as outlined in Company Submission Document B Section B.3.3.1.1
Abbreviations: AIC, Akaike information criterion; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TTP, time to progression

Table 4: Scenario analysis: alternative chemotherapy extrapolations - adult population (with PAS)

Chemotherapy TTP extrapolation (ordered by AIC)	NIVO + IPI versus Chemotherapy		
	Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
Lognormal	[redacted]	[redacted]	£1,736
Generalised Gamma	[redacted]	[redacted]	£1,836
Log-logistic	[redacted]	[redacted]	£1,764
Gamma	[redacted]	[redacted]	£1,746
Exponential	[redacted]	[redacted]	£1,735
Weibull	[redacted]	[redacted]	£1,743
Gompertz	[redacted]	[redacted]	£1,967

Abbreviations: AIC, Akaike information criterion; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; TTP, time to progression

More complex models in the form of 1- and 2-knot spline models were originally not considered, as the standard parametrisations were considered appropriate. However, six spline models have been investigated and compared to the generalised gamma fit. Table 5 summarises the AIC and BIC values of the standard parametric fits alongside six spline models fit to the CM8HW NIVO + IPI TTP data. While generalised gamma

was the lowest AIC and BIC among the standard parametric models, the 2-knot spline models have lower AIC and BIC statistics.

Table 5: CM8HW NIVO + IPI TTP AIC values – standard parametric and spline models (lowest AIC in bold)

TTP	CM8HW NIVO + IPI AIC	CM8HW NIVO + IPI BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]
Log normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Spline hazard 1	[redacted]	[redacted]
Spline hazard 2	[redacted]	[redacted]
Spline odds 1	[redacted]	[redacted]
Spline odds 2	[redacted]	[redacted]
Spline normal 1	[redacted]	[redacted]
Spline normal 2	[redacted]	[redacted]

Extrapolations for the six spline models compared against the generalised gamma can be found in Figure 1 and Figure 2. The generalised gamma was comparable in both the observed and extrapolated time frame to the single knot splines and the two-knot hazard spline. The two-knot normal spline and two-knot odds spline fit provide a tighter fit to the early part of the observed period. However, as noted above, this can be expected of spline models and this should be viewed in the context of the limitations noted above and in the published literature (Latimer, et al., 2022).

Figure 1: CM8HW NIVO + IPI TTP spline fits to end of trial period

Figure 2: CM8HW NIVO + IPI TTP spline fits beyond trial period

Table 6 summarises the AIC and BIC values of the six spline models fit to the CM8HW chemotherapy TTP data. Several spline models have AIC slightly lower than that for the generalised gamma extrapolation (687.4); however, all are broadly similar.

Table 6: CM8HW chemotherapy TTP AIC values – standard parametric and spline models (lowest AIC in bold)

TTP	CM8HW chemotherapy AIC	CM8HW chemotherapy BIC
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]
Log normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Spline hazard 1	[redacted]	[redacted]
Spline hazard 2	[redacted]	[redacted]
Spline odds 1	[redacted]	[redacted]
Spline odds 2	[redacted]	[redacted]
Spline normal 1	[redacted]	[redacted]
Spline normal 2	[redacted]	[redacted]

Extrapolations for the six spline models compared against the generalised gamma can be found in Figure 3 and Figure 4. The generalised gamma was comparable with all spline models.

Figure 3: CM8HW chemotherapy TTP spline fits to end of trial period

Figure 4: CM8HW chemotherapy TTP spline fits beyond trial period

A scenario analysis was undertaken using the 2-knot odds spline model for both NIVO + IPI and chemotherapy. This survival curve was chosen as it provided a closer fit to observed NIVO + IPI data from CM8HW and provided one of the more optimistic fits for the chemotherapy arm.

Scenario analysis outcomes are provided in Table 7. As can be seen, in the NIVO + IPI arm, LYs and QALYs are decreased versus the base case analysis (versus LYs and versus QALYs), with costs also slightly decreased versus). In the PEMBRO arm, an increase in costs compared with the base case (versus) and decreased LYs and QALYs (versus LYs and versus QALYs) furthers the dominance of NIVO+IPI over PEMBRO. Marginal impacts in the costs and QALY outcomes for chemotherapy compared with base case results in limited impact on the ICER and cost-effectiveness conclusions are unchanged.

Table 7: Scenario analysis: 2-knot odds spline TTP (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI		[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)		[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)		Dominant	£1,986

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B11. Please provide the PrePS data from the CM142 study as mentioned in the submission.

Response

PrePS from CM142 is provided within Document B Section B.3.9.3.1.2 and Appendix O Section 3.2.4 of the company submission. Additionally, this data has been used within the economic model as a scenario analysis, where impact was limited. This has been reproduced below for ease of reference.

There was a total of 164 patients used to inform this analysis (Cohort 2 [2L+ NIVO + IPI]: 119 patients; Cohort 3 [1L NIVO+IPI]: 45 patients), all of which received NIVO + IPI (Figure 5). The median time to death was not reached and the one-year survival probability was [redacted] (95% CI: [redacted]).

Figure 5: CM142 cohorts 2 and 3 pre-progression survival Kaplan-Meier data

As previously mentioned, there were few events so that the data can be considered extremely immature and should be viewed with caution, as evidenced by Figure 6.

As previously described for the TTP survival analysis, the best model fit was selected based on the model selection algorithm outlined in Palmer et al. (2023) as well as via statistical tests such as AIC. The lognormal model is recommended based on low AIC value and plausible long-term extrapolation. For this scenario analysis, the economic model applies this data in addition to general population mortality.

Figure 6: CM142 cohort 2 (2L+ NIVO + IPI) and 3 (1L NIVO + IPI) PrePS standard parametric fits beyond trial period

Results are provided in Table 8. Total LYs and QALYs are decreased across all modelled treatment arms due to increased deaths from the progression-free state. However, this results in lower resource use for NIVO + IPI and PEMBRO, so that ICERs are relatively unchanged versus PEMBRO and are dominant versus chemotherapy.

Table 8: Scenario analysis - CM142 for PF-D transition - adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI		[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)		[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)		Dominant	£2,036

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B14. The economic model uses pooled utility data for the progressed disease health state justified by "poor completion rates and censoring following subsequent treatment."

Please provide a scenario where the analysis is re-run by counting subsequent treatment as an event for progression, and then apply the results of the arm-specific analysis.

Response

An analysis was conducted where patients who switched treatment were removed from the PF utility value. Values are provided in Table 9 below.

Results are provided in Table 10. As can be seen, total QALYs are increased across the PEMBRO and chemotherapy modelled treatment arms; however, NIVO + IPI maintains an overall benefit over PEMBRO and chemotherapy. As a result, ICERs remain below a £30,000/QALY willingness-to-pay threshold.

Table 9: Utility values applied for base case analysis and scenario analysis, with comparison to previous HTAs

		Progression-free	Progressed
Base case analysis	NIVO + IPI/PEMBRO	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
Scenario analysis	NIVO + IPI/PEMBRO	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
TA709 (N-177)	PEMBRO	0.843	0.730
	Chemotherapy	0.787	0.730
TA439	Cetuximab, panitumumab and chemotherapy	0.767	0.64

Table 10: Scenario analysis: alternative utility values - adult population (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	-	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	-	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B16. Please add a scenario that uses trial weighting for chemotherapy rather than ad-board opinion used for the proportion of patients receiving regimens in Table 82.

Response

Table 11 shows the chemotherapy split in CM8HW, which has been reweighted to exclude bevacizumab, as this is not recommended for use by NICE (2012; TA242). This has been applied within the economic model as outlined in Table 12.

Table 11: Chemotherapy regimen split in CM8HW trial and after exclusion of bevacizumab regimens.

	mFOLFOX6	FOLFIRI	mFOLFOX6 + cetuximab	FOLFIRI + cetuximab	mFOLFOX6 + bevacizumab	mFOLFIRI + bevacizumab
CM8HW	10.2%	13.6%	5.7%	6.8%	42.0%	21.6%
Reweighted	28.10%	37.47%	15.70%	18.73%	-	-

This adjusted split increased the cost of chemotherapy from £[redacted] Q2W in the base case to £[redacted]. This increase is mainly due to the increased use of cetuximab-based regimens.

When using the chemotherapy regimens and the splits from above, NIVO + IPI treatment results in QALY gains relative to comparators at a lower cost, thus being dominant Table 11.

Table 12: Summary of results when chemotherapy split from CM8HW is used (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI		[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)		[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)		[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B18. Please include drug wastage in the model using European patient weights or weight data for the UK general population if trial data is not available / the sample size is too small. Please use method of moments to accurately account for wastage.

Response

The mean patient age in the CM8HW trial was 60.9 years old. Therefore, the mean weight, standard error and sample size for women and men in the age group 55-64 reported in the Health Survey for England 2021 were used in this scenario to better reflect the mean weight of patients in England and the impact on drug costs (NHS Digital, 2022). Previous studies have demonstrated that the general population may have indistinguishable characteristics to patients with several conditions (including multiple cancers) (Hatswell et al., 2016). In order to capture the effect of variable weights, a log-normal distribution has been fitted, separately for men and women and 100,000 patients' weights (53,795 women and 46,205 men samples representing the gender split in the CM8HW) have been sampled. A log-normal distribution has been shown in previous work to be the best fit to the distribution of patients' characteristics (weight) (Hatswell et al., 2016). The data used to derive the standard deviation (SD) and the resulted scaled mean and scaled SD are shown below (Table 13).

Table 13: Summary of parameters used to sample from log-normal distribution

Patients	Mean	SE	SD*	Sample size	Scaled mean**	Scaled SD**
Male	87.73	0.75	16.79	495	4.46	0.19
Female	74.18	0.79	18.74	557	4.28	0.25

Abbreviations: SD, standard deviation; SE, standard error;
SD calculated as: SE√Sample size
**Scaled mean: ln (mean^2 / √ (mean^2 + SD^2))
**Scaled SD: √ (ln((mean^2 + SD^2) / mean^2))

Dosage of ipilimumab- and panitumumab-based regimens is dependent on patients' weight. As such, the 100,000 samples weights were divided by 50 ml (vial dose), to determine the number of ipilimumab vials needed, then multiplied by the cost of a vial and averaged across the cohort, resulting in a cost of [redacted] per administration. This is slightly higher than the cost used in the base case ([redacted]).

Panitumumab is administered with a dosage of 6mg/kg body weight, therefore the sampled weights were multiplied by 6, then divided by the vial dose and multiplied by the cost of vial, and averaged across the cohort, resulting in a cost of £2,022. This is slightly higher than the base case costs of £1,896, thus increasing the costs of chemotherapy.

The impact of these changes on the cost-effectiveness results is illustrated in Table 14. NIVO + IPI dominates PEMBRO regimen, and is cost-effective against chemotherapy, with an ICER below the WTP threshold.

Table 14: Scenario analysis: alternative patient weights (with PAS)

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs versus NIVO + IPI	-	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI (£)	-	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B19. PRIORITY QUESTION. Please provide a scenario that includes subsequent therapy for patients who initially received NIVO+IPI, PEMBRO and chemotherapy, based on data from clinical trials.

Response

CM8HW and CM142 only track specific subsequent treatments received, as opposed to treatment regimens. Table 15 provides available evidence on which treatments have been prescribed as a subsequent treatment within CM8HW.

Table 15: CM8HW subsequent therapies

Subsequent systemic therapy, n (%)	NIVO + IPI (n = 202)	Chemo (n = 101)
Any systemic therapy	[redacted]	[redacted]
On study crossover to NIVO + IPI	[redacted]	[redacted]
Non study systemic therapy	[redacted]	[redacted]
Anti-CTLA4	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Anti-PD-1 or anti-PD-L1	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Camrelizumab	[redacted]	[redacted]
Tislelizumab	[redacted]	[redacted]
EGFR inhibitors	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]
Platinum compounds	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]
VEGFR targeted therapy	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Aflibercept	[redacted]	[redacted]
Other systemic therapies	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Irinotecan hydrochloride	[redacted]	[redacted]
Raltitrexed	[redacted]	[redacted]
Trifluridine/tipiracil	[redacted]	[redacted]
MEK, NRAS and BRAF inhibitor	[redacted]	[redacted]
Encorafenib	[redacted]	[redacted]

Patients may have received more than 1 type of subsequent therapy

Subsequent treatments are reported within TA709 for KEYNOTE-177 (Table 16). However, these included several regimens that are not available within UK clinical

practice in the treatment experienced mCRC setting, including cetuximab and bevacizumab. As a result, TA709 applied subsequent treatment distribution based on clinical opinion.

Table 16: Subsequent treatment distributions as per KEYNOTE-177 (adapted from TA709 company submission Table 57)

Subsequent treatments, %	Pembrolizumab	Standard of care
No treatment	46.3	16.8
FOLFOX	13.2	6.9
FOLFIRI	10	8.2
Cetuximab + FOLFOX	1.6	0
Cetuximab + FOLFIRI	1.3	0
Bevacizumab + FOLFOX	15.6	30.9
Bevacizumab + FOLFIRI	11.9	37.1

FOLFIRI: fluorouracil, folinic acid and irinotecan; FOLFOX: fluorouracil, folinic acid and oxaliplatin

In order to address this request, data from KEYNOTE-177 and CM8HW were used to develop a subsequent treatment distribution based on clinical trials but relevant to clinical practice. Subsequent treatment in the NIVO+IPI and PEMBRO arms was based on the PEMBRO arm of KEYNOTE-177, reweighted to exclude bevacizumab and cetuximab. Immunotherapy as a subsequent therapy in the modelled chemotherapy arm was based on usage in the chemotherapy arm of the CM8HW study (NIVO+IPI: [redacted]/101 patients, [redacted] patients as crossover and [redacted] patients outside of study protocol; PEMBRO: [redacted]/101 patients). The remaining patients are assumed to receive chemotherapy, reweighted based on subsequent treatments in the chemotherapy arm of KEYNOTE-177 (excluding bevacizumab and cetuximab).

Table 17: Subsequent treatments applied in scenario

Subsequent treatments	Modelled treatment arm		
	NIVO+IPI	PEMBRO	Chemotherapy
FOLFOX	56.90%*	56.90%*	[redacted]
FOLFIRI	43.10%*	43.10%*	[redacted]
NIVO+IPI	-	-	[redacted]
PEMBRO	-	-	[redacted]

* Informed by PEMBRO arm of KEYNOTE-177, reweighted to exclude bevacizumab and cetuximab

† Informed by immunotherapy use in CM8HW.

‡ Remaining patients receive chemotherapy aligned with chemotherapy arm of KEYNOTE-177 (excluding bevacizumab and cetuximab)

These subsequent treatment distributions were applied in two scenarios: one applied post-progression survival in the chemotherapy arm aligned with submission base case analysis, while the other used post-progression survival as in question B21a.

Table 18 provides outcomes for the scenario assuming post-progression survival as in the submission base case analysis. There is a slight decrease in subsequent treatment costs in the NIVO + IPI and PEMBRO arms, with limited impact on total costs. By contrast, there is a substantial increase in subsequent treatment costs in the chemotherapy arm, resulting in total costs increasing from [redacted] to [redacted]. However, the resulting ICER remains cost-effective for NIVO + IPI.

Table 18: Scenario analysis - Trial-based subsequent treatment with post-progression survival in chemotherapy arm aligned with submission base case analysis

	NIVO + IPI	PEMBRO	Chemotherapy
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI		[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)		[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)		[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 19 provides outcomes using OS data from CM142 cohort 2 (2L+ NIVO + IPI) to inform the chemotherapy arm post-progression survival. Given that NIVO + IPI use is reduced to less than 50% in this scenario, use of this survival lacks face validity. However, the outcomes are provided for completeness. Subsequent treatment costs in the chemotherapy arm are increased against the base case analysis due to inclusion of pembrolizumab and longer time on treatment, as more patients remain alive for longer in the progressed disease state. As a result, NIVO + IPI is dominant versus chemotherapy in this scenario.

Table 19: Scenario analysis - Trial-based subsequent treatment with post-progression survival in chemotherapy arm aligned with B21a

	NIVO + IPI	Chemotherapy

Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI	[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)	[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)	-	Dominant

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

B20. Please justify not presenting cost-effectiveness analysis according to mutation status given the chemotherapy comparator differs.

Response

In the CM8HW subgroup analysis, the HR for progression in the KRAS-mutation (subgroup n=45) was similar to the HR (95% CI) for the whole centrally-confirmed population 0.24 [0.09, 0.63] vs. 0.20 [0.14, 0.31]). KRAS mutation appear to have no significant impact on the comparative efficacy of NIVO + IPI. Additionally in the base case the use of the different types of chemotherapy regimens/mutation status are weighted according to the proportion of patients receiving each regimen in the experience of UK clinical experts attending a BMS UK advisory board (see table 82).

Table 82 (of Document B): Total weighted chemotherapy costs per model cycle

Regimen	Advisory board opinion	Proportion weighting
FOLFOX	87.5%	29.17%
FOLFIRI		29.17%
CAPOX		29.17%
Capecitabine	0%	0% (assessed in scenario)
FOLFOXIRI	5%	5%
FOLFOX + cetuximab	7.5%	1.875%
FOLFIRI + cetuximab		1.875%
FOLFOX + panitumumab		1.875%
FOLFIRI + panitumumab		1.875%

Below we present the cost-effectiveness for adults when 100% of chemotherapy patients are allocated to the relevant chemotherapy regimen in Table 20 to Table 35. The result show that in all cases; RAS mutation, EGFR expressing RAS wild type mutation, non-EGFR expressing mutation and other non-mutation specific

treatments, NIVO + IPI is very cost-effective compared to chemotherapy with and without PAS (PAS = Dominant to £2,361 per QALY, without PAS = [redacted] to [redacted] per QALY).

The following analyses assumes no change in efficacy as in the CM8HW subgroup analysis, the HR for progression in the KRAS-mutant subgroup was similar to the HR for the whole population. Chemotherapy drug acquisition costs will be assumed to be 100% usage of the regimen allocated to each mutation type in sections A to Fiii.

A. Chemotherapy is 100% FOLFOXIRI for the RAS mutation

Table 20: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,282

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 21: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

B. Cetuximab with FOLFOX for EGFR expressing RAS wild type mutation

Table 22: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 23: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYG: life years gained; LYs: life years; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

C. Cetuximab FOLFIRI for EGFR expressing RAS wild type mutation

Table 24: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 25: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

D. Panitumumab with FOLFOX for RAS wild type EGFR expressing and non-EGFR expressing mutations

Table 26: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 27: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

E. Panitumumab FOLFIRI for RAS wild type EGFR expressing and non-EGFR expressing mutations

Table 28: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 29: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

F. Other chemotherapy treatments in the standard of care arm (no mutation).

i. MFOLFOX6

Table 30: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,361

Costs and QALYs discounted; LYs undiscounted.

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 31: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

ii. FOLFIRI

Table 32: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,307

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 33: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

iii. CAPOX

Table 34: Adult population (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,450

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

Table 35: Adult population (no PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	NIVO + IPI ICER (£/QALY)
NIVO + IPI	[redacted]	[redacted]	[redacted]				
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs and QALYs discounted; LYs undiscounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs: life years; LYG: life years gained; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

B21. PRIORITY QUESTION: It does not appear reasonable to assume equal PPS for all arms given that different options are available for subsequent treatment (e.g. nivo+ipi is available after chemotherapy and not after nivo+ipi).

a) Please provide an analysis using data from your later line trial to inform subsequent treatment as an alternative analysis or to replace the base case post chemotherapy.

Response

OS data from CM142 cohort 2 (2L+ NIVO + IPI) was used to derive an exponential log rate ([redacted]) to inform a scenario analysis. As patients in the chemotherapy arm would be living for a long period in the progressed disease state, BSC costs were no longer

appropriate to apply for the entirety of that time. As a result, BSC costs were removed from the analysis in order to provide an unbiased scenario.

Outcomes from this analysis are provided in Table 36; disaggregated results are provided in Table 37 to ensure transparency and support face validity.

Use of CM142 OS increased LY accrual in the progressed disease state to [redacted], resulting in a total of [redacted] LYs. This is slightly below the total LYs reported for the second-line NIVO + IPI arm in the company submission for TA716 ([redacted] LYs) (NICE, 2021b) but retains face validity when viewed within a treatment pathway using first-line chemotherapy. QALY accrual was also increased in the progressed disease state, increasing from [redacted] to [redacted], which is comparable with total QALYs from the company submission in TA716 ([redacted]) (NICE, 2021b).

Longer use of second-line NIVO + IPI in the chemotherapy arm also increased total costs of subsequent treatment, from [redacted] in the base case to [redacted] in the scenario. This reflects longer time on treatment, as more patients remain alive for longer in the progressed disease state.

As a result of these changes, NIVO + IPI is dominant versus chemotherapy in this scenario.

Table 36: Scenario analysis: CM142 cohort 2 OS as PD-D transition (with PAS)

	NIVO + IPI	Chemotherapy
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI		[redacted]
Incremental costs versus NIVO + IPI (£)		[redacted]
ICER versus NIVO + IPI (£/QALY)		[redacted]

Costs and QALYs discounted; LYs undiscounted
Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 37: Scenario analysis: CM142 cohort 2 OS as PD-D transition (with PAS) - disaggregated outcomes

	NIVO + IPI	Chemotherapy
Clinical outcomes		
QALYs (discounted)	[redacted]	[redacted]
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Disutility of grade 3-4 AE	[redacted]	[redacted]
Life years (undiscounted)	[redacted]	[redacted]
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Cost outcomes (discounted)		
Total Costs	[redacted]	[redacted]
Treatment-related costs	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]
Total resource use	[redacted]	[redacted]
Resource use	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]

Bold italicised values are updated from base case analysis.

BSC costs removed from analysis to ensure face validity.

b) Please comment on the applicability of data from CM-142 to pembrolizumab based on how similar (or not) the subsequent treatments received in CM-142 are to those in KN-177 and how similar the treatments expected to be received in practice after these two therapies are.

Response

BMS do not have access to details about the subsequent therapy in KN177, however it has been published (Helwick, 2021) that 28.8% of patients in the pembro arm received subsequent therapy, primarily with oxaliplatin-based regimens. In NICE TA709 clinical experts explained that the KN177 trial included cetuximab as a subsequent therapy. 7 patients received pembrolizumab again,

some as per protocol for disease relapse after completion of 2 years of first-line pembrolizumab.

In cohort 3 of CM142, six patients received subsequent systemic therapy. The most common subsequent systemic therapies were 5FU regimens in 8.9% of patients (n=4). Oxaliplatin, cisplatin or irinotecan were used in 6.7% of patients (n=3). VEGF inhibitors (bevacizumab, aflibercept, ramucirumab) were used in 6.7% patients (n=3). Only 1 patient received nivolumab as a subsequent therapy in CM142 compared to 7 patients receiving an immuno-oncology treatment in KN177.

The limited detail available for KN177, and small numbers of subsequent systemic therapies in CM142 limit conclusions around similarity between the trials or to UK clinical practice. The two trials were similar in their subsequent therapy in that chemotherapy was the most common subsequent systemic therapy. This would also reflect clinical practice in the UK. The use of 2L VEGF, eGFR and immunotherapy agents after 1L immunotherapy in both trials does not reflect UK practice, as these are not approved in this setting according to NICE TA242.

c) **We heard from a clinical expert that around 50% of patients get pembrolizumab rather than nivolumab + ipilimumab as subsequent treatment post chemotherapy as they are unsuitable for treatment with the doublet. Please provide a scenario analysis assuming this allowing for the difference in effectiveness between the two treatments or provide alternate data on what proportion get each option 2nd line.**

Response

In this scenario analysis patients that received first line treatment with chemotherapy are assumed to receive second line treatment with NIVO + IPI or pembro (50% receiving each immune-oncology option). Outcomes from this analysis are provided in Table 38; disaggregated results are provided in Table 39 to ensure transparency and support face validity. Use of pembrolizumab increased total costs of subsequent treatment to [redacted] in this scenario. This reflects the higher cost of pembrolizumab in the absence of the PAS. NIVO + IPI remains dominant versus chemotherapy in this scenario.

It is unclear if it is plausible to assume that up to 50% of patients are unable to receive NIVO + IPI. As such, a scenario analysis has been conducted to assess the impact of different thresholds of pembrolizumab use (05 to 50%), which has been provided in Table 40. In all cases NIVO + IPI remains dominant versus chemotherapy.

Table 38: Scenario analysis: CM142 cohort 2 OS as PD-D transition and pembrolizumab and NIVO + IPI as subsequent therapy (with PAS)

	NIVO + IPI	Chemotherapy
Total costs	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI		[redacted]
Incremental costs versus NIVO + IPI (£)		[redacted]
ICER versus NIVO + IPI (£/QALY)		[redacted]

Costs and QALYs discounted; LYs undiscounted

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PEMBRO: pembrolizumab; QALYs, quality-adjusted life years

Table 39: Scenario analysis: CM142 cohort 2 OS as PD-D transition and pembrolizumab and NIVO + IPI as subsequent therapy (with PAS) - disaggregated outcomes

	NIVO + IPI	Chemotherapy
Clinical outcomes		
QALYs (discounted)	[redacted]	[redacted]
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Disutility of grade 3-4 AE	[redacted]	[redacted]
Life years (undiscounted)	[redacted]	[redacted]
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Cost outcomes (discounted)		
Total Costs	[redacted]	[redacted]
Treatment-related costs	[redacted]	[redacted]
Drug acquisition	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]
Adverse Events	[redacted]	[redacted]
Total resource use	[redacted]	[redacted]
Resource use	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]

Bold italicised values are updated from base case analysis.

BSC costs removed from analysis to ensure face validity.

Table 40: Scenario analysis: CM142 cohort 2 OS as PD-D transition and pembrolizumab and NIVO + IPI as subsequent therapy (with PAS) – pembrolizumab threshold analysis

NIVO + IPI proportion (%)	Pembrolizumab proportion (%)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
50%	50%	[redacted]	[redacted]	Dominant
60%	40%	[redacted]	[redacted]	Dominant
70%	30%	[redacted]	[redacted]	Dominant
80%	20%	[redacted]	[redacted]	Dominant
90%	10%	[redacted]	[redacted]	Dominant
100%	0%	[redacted]	[redacted]	Dominant

D1. What is the reason the model looks at PrePS independently rather than predicting PFS and calculating PrePS as PFS - TTP as is done in TA709?

Response

Due to data immaturity, OS and other secondary endpoints were not tested in the interim CM8HW analysis, as per the hierarchical testing strategy pre-defined in the trial protocol. As such, it was not permissible to assess mortality data from the CM8HW within the economic analysis. As CM8HW mortality is not available, independent sources were required. General population mortality was used to inform pre-progression mortality within the base case analysis. This approach was validated during a global advisory board, which included economists and clinical experts, as well as a UK-specific advisory board, where it was considered appropriate.

Further, the model outputs validate well against CM8HW PFS data for the NIVO + IPI, as shown in Table 41, the economic model increased PFS in the chemotherapy arm, this will lead to cost-effectiveness outcomes favouring chemotherapy, meaning that the ICERs for NIVO+ could be considered conservative.

Table 41:Comparison of CM8HW PFS and economic model progression free state occupancy

	NIVO + IPI		CHEMO	
	CM8HW PFS[1]	Economic model progression free occupancy	CM8HW PFS[1]	Economic model progression free occupancy
One year	71.15%	[redacted]	23.70%	[redacted]
Two years	[redacted]	[redacted]	[redacted]	[redacted]

Additionally, a scenario analysis was conducted where data from CheckMate 142 was used to inform this input (Company submission, Document B Section B.3.9.3.1.2). Table 42 shows a comparison between this scenario analysis and the base case analysis, demonstrating that applying general population mortality may be considered the more conservative approach compared with using CheckMate 142 inputs.

Table 42: Submission base case analysis compared with scenario analysis applying CM142 for PF-D transition (with PAS)

	Base case analysis			Scenario analysis		
	NIVO + IPI	PEMBRO	Chemo	NIVO + IPI	PEMBRO	Chemo
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs versus NIVO + IPI		[redacted]	[redacted]		[redacted]	[redacted]
Incremental costs versus NIVO + IPI (£)		[redacted]	[redacted]		[redacted]	[redacted]
ICER versus NIVO + IPI (£/QALY)		Dominant	£1,836		Dominant	£2,036

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

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	Bowel Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are the UK's leading bowel cancer charity. We are determined to save lives and improve the quality of life of everyone affected by bowel cancer by championing early diagnosis and ensuring access to best treatment and care. We support and fund targeted research, provide expert information and support to patients and their families, educate the public and professionals about the disease and campaign for early diagnosis and access to best treatment and care. Most of our income is generated from individual, corporate and trust fundraisers. A small proportion of our income (~1.4%) was given by pharmaceutical companies in support of generating Health Information and Support packages for patients and our wider community.
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.**	Yes, in 2023 we have received £10,323.30 in funding from a comparator treatment company (Merck) with the purpose of generating Patient Information and Support packages, including a Newly Diagnosed Information Pack.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information provided in this response was gathered from a survey of people with untreated unresectable or metastatic colorectal cancer with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR). The survey was conducted by Bowel Cancer UK over two-week period and was designed according to the consultation questions, with the language adjusted to ensure that it was lay friendly. The survey was disseminated to our community through our online forum groups.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of bowel cancer is life changing, not only for the individual diagnosed but also for their family and loved ones. Such experiences are even more acute for those diagnosed at a later stage whereby we know that bowel cancer is harder to treat, and the chance of survival is low. Patients experience numerous challenges across the pathway, from initial diagnosis, to treatment, and care. Specifically, these challenges relate to the impact and reality of an advanced bowel cancer diagnosis, the difficulty and complexity in navigating treatment and care pathways and the impact treatment can have on a person's quality of life. In our survey, patients described living with these types of advanced bowel cancer as "**unstable**", "**very difficult**", and "[an] **emotional roller coaster**". One respondent described having a "**constant fear** that your illness will be terminal and that you will **die soon** and there is **nothing you can do about it**", whilst another said that they are "living [from] scan to scan and **always in fear** that you may have to start another treatment or run out of options". These sentiments reflect the feeling amongst some respondents that they had few options left, with one even saying that they felt that the people caring for them wanted them to "**just go away and die**". Moreover, respondents also highlighted the negative impact of these types of bowel cancer on their family. For example, one patient said that whilst they try to stay 'positive', the realities of advanced bowel cancer meant both they and their husband were finding things difficult, with the latter finding things particularly hard as they have "no [other] family members to share the load". In a similar vein, another patient highlighted the detrimental effects of their experiences on their children and the instability this created around their everyday lives.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Survival rates for advanced bowel cancer are poor, with less than one in ten people surviving more than five years. These patients deserve access to the best quality treatment and care. For some patients these drugs can be lifesaving, while for others they can prolong life, resulting in more time to spend with loved ones. Therefore, it is essential patients gain timely access to the treatments that their clinicians feel could benefit them. Unfortunately, many patients spoke of their frustration at the current treatment options and care available on the NHS. One said that their cancer team 'fobbed' them off to their GP to address issues with side effects of standard chemotherapy treatments, adding that there was a "lack of joined up care" between their cancer MDT and GP meaning that – when it came to knowing what treatments were available – they were "left to find out half the stuff" themselves. A second patient described the feeling that their oncologist has "always written [them] off", noting how – despite their MDT recommending aggressive chemotherapy – they only received three months on Capecitabine, were not offered Avastin with Lonsurf even when they offered to pay for it privately, and were eventually told that "no more treatment was available" for them. They also highlighted contradictory medical opinions regarding treatment options between their oncologist and other health professionals such as their GP and a second oncologist. Other patients recounted more positive experiences – most of which were associated with this technology. One spoke of having a "good experience" regarding an unnamed treatment (assumed to be Nivolumab with Ipilimumab) that was supplied via compassionate use and which the NHS administered. Another – who noted that they had previously had metastatic colon cancer – said that their experience of being treated with Nivolumab combined with Ipilimumab was 'excellent' and they have had no signs of cancer five years on.
8. Is there an unmet need for patients with this condition?	Our organisation believes that there is a clear unmet need for these patient populations due to a severe lack of available treatment options on the NHS. This feeling was reflected in our survey, with several patients highlighting similar experiences of confusion and frustration regarding the best treatment pathways leading to feelings of "false hope" and a sense that they were not being listened to. Some patients also highlighted the issue of being bounced around between different healthcare professionals due to a lack of understanding of the options available for these types of bowel cancer within the medical community.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Several patients cited the benefits of Nivolumab combined with Ipilimumab compared to standard treatment options, with one highlighting the potential improvements in "quality of life [compared to] chemotherapy or surgery", and another noting how "immunotherapy has much lighter [and] easier to manage side effects in most cases", with the 'ease' of immunotherapy regimens in comparison to chemotherapy viewed as "a very big advantage". Moreover, respondents highlighted the likely increased efficacy of this technology, with one patient pointing out that they would accept "any side effects to have the opportunity to have any treatment that 'might' help", and another citing the potential benefits and hope that personalised medicines such as this technology offer. These claims align with the clinical view that bowel cancer patients with the molecular features of deficient mismatch repair (dMMR) generally experience better responses to immunotherapy regimens such as immune checkpoint inhibitors compared to those who have proficient mismatch repair (pMMR).

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients cited several possible disadvantages of Nivolumab combined with Ipilimumab compared to standard treatment options, pointing to potential experiences of "neuropathy", "tiredness", and "skin problems", as well as unknown long-term issues.

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.	Regarding those that may benefit more from Nivolumab combined with Ipilimumab, these groups were highlighted: people with late-stage bowel cancer and who are in palliative care, and people who have tumours that show molecular features of dMMR or MSI-H. For the former, this technology was viewed as potentially valuable for improving quality of life within a palliative care pathway by potentially extending time with loved ones and by making these experiences more tolerable compared to alternative options. Whilst for the latter, this technology was viewed as a more effective treatment compared to standard treatment pathways due to the molecular features of dMMR and MSI-H tumours, with people with Lynch syndrome cited as the main beneficiaries. No distinction was made between somatic and germline variations in dMMR, so it is assumed that these respondents were referencing both. Regarding those who may benefit less from this technology, one group that was identified was those people whose immune system is compromised and therefore may experience an increased risk of contracting an illness during this treatment pathway.

Equality

12a. Are there any potential equality issues that should be taken into account when considering this condition and the technology? **Please consider if there are any potential equalities issues related to treatment in young people aged 12 to 17 years.**	Overall, patients did not highlight any equality issues to be considered with this technology. One noted that if a person is “fit enough [and] has a positive mindset, [then] they should be able to take the opportunity to have this treatment”. Whilst another made the distinction between fairness and equality, arguing that the former should take precedence when considering a treatment modality such as this technology. The issue of young people aged 12 to 17 years did not generate any substantive engagement beyond responses such as ‘not sure’ and ‘unknown’.

Other issues

13. Are there any other issues that you would like the committee to consider?	A couple of patients highlighted the potential value of using nivolumab and ipilimumab as a treatment modality for these types of bowel cancer at the "earliest possible stage before [the] cancer spreads". Whilst another argued that patients with these types of bowel cancer should have the ability to request for nivolumab and ipilimumab as a treatment option even if a presiding healthcare professional does not wish to pursue this treatment pathway.
14a. Would you expect there to be any difference in the treatment effect of nivolumab with ipilimumab in adults and in young people aged 12 to 17 years? **14b. Would you expect there to be any difference in the short- or long-term adverse event profile from nivolumab with ipilimumab in adults and in young people aged 12 to 17 years?** **14c. What current treatments are used for treating unresectable or metastatic colorectal cancer with high-**	Again, the issue of young people aged 12 to 17 years did not generate any substantive engagement beyond responses such as 'not sure' and 'unknown'.

microsatellite instability or mismatch repair in young people aged 12 to 17 years? **14d. Are there any other important differences in care for young people aged 12 to 17 years compared with adults which the committee should be aware of?**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• A diagnosis of bowel cancer can be life changing for those diagnosed, as well as their friends and family, and is even more acute for those diagnosed at the later stages whereby it is harder to treat and there is a low chance of survival. • Current treatment options approved for use on the NHS for these types of advanced bowel cancer are extremely limited, with many patients unable to access a treatment that could prolong their life, leading to experiences of fear, instability, and general hopelessness for them and their families. • Patients highlighted the potential benefits of this technology in comparison to standard treatment pathways, with the 'ease', improved quality of life, and efficacy of immunotherapy treatments offering greater hope and choice. • Patients felt that those who have late-stage bowel cancer and are in palliative care, and those who have tumours with molecular features of dMMR (somatic or germline) would benefit most from this treatment. • If outcomes for people with advanced bowel cancer are to improve, a one-size fits all approach to treating people with the disease will not work. Rather, all patients should have access to precise and personalised treatment modalities that are most suitable for them.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Clinical expert statement

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 you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Wednesday 20 November 2024.** 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, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Jenny Seligmann
2. Name of organisation	University of Leeds
3. Job title or position	Professor of Gastrointestinal Oncology and Honorary Consultant Medical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency? ☒ A specialist in the clinical evidence base for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would 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.	☐ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil
8. What is the main aim of treatment for untreated unresectable or metastatic colorectal cancer 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)	The main aim is primarily to improve survival rates but in the first instance to stop progression. However, in a sub-set of these cancers patients will have a complete response to treatment and may be cured; others will benefit from a prolonged period of progression free survival. Therefore the impact of overall survival from immunotherapy is not yet realised as there has been few events and cross-over of the control arms. The use of PFS and response in this situation is very reasonable.
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)	Extension of PFS – for example 50% of patients being progression free at 1 year. However complete responses in a smaller proportion is also clinically meaningful as it is potentially curative.
10. In your view, is there an unmet need for patients and healthcare professionals in untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency?	Yes – prior to immunotherapy this group of patients had a poor prognosis with little effective treatment. Immunotherapy has transformed the outlook, offering cure to a proportion of patients. The current 1st line treatment of PD-1 alone has had a big impact but the Keynote 177 trial demonstrated that a third of patients experienced disease progression in the 1st 12 weeks of immunotherapy treatment – this group had a worse outlook than those treated with chemotherapy. The current 2nd line use of nivolumab and ipilimumab requires 1st line treatment with chemotherapy; we know responses to chemotherapy are limited in the MSI-H group plus many patients will not progress to 2nd line treatment. This is therefore not commonly utilised. There is therefore an urgent need to optimise 1st line management to maximise the chances of good response and hence increase the number of patients who will have prolonged disease stability or even cure.

11. How is untreated unresectable or metastatic colorectal cancer 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?	In the UK it is most common practice to await MSI or MMR testing prior to starting treatment in mCRC. This is advocated by treatment guidelines. Most patients with MSI-H disease will commence treatment with pembrolizumab. In general the ESMO Guidelines are most commonly referenced in the UK, plus guidance from NICE around the approval. Some clinicians will commence patients with chemotherapy with a plan to use 2nd line immunotherapy. This tends to be in the patients where there is concern for primary progression on immunotherapy (high volume of disease, symptomatic). However we do not have data from Keynote 177 to highlight which patients are at most at risk of primary progression. If Nivolumab and ipilimumab was approved then this would almost certainly be the upfront treatment of choice for good performace status patients due to the higher chance of upfront response and favourable PFS rates compared with PD-1 alone. It is likely that patients who are frailer or older will continue to receive PD-1 alone.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • 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)	Nivo/ ipi will be used in the first line treatment rather than the 2nd line (which is currently available). It should only be used in a specialist clinic. No specific additional investment should be required compared to current SOC as immunotherapy is already available in 1st line settings and centres who deliver this have set pathways for toxicity management. I would recommend that the company deliver specific educational opportunities around toxicity managenment to HCPs that deliver CRC as most experience is with PD-1 alone.

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 – this was clearly demonstrated in the CheckMate 8HW trial. The PFS rate of 72% at 2 years is unprecedented for mCRC and is notably higher in the trial testing PD-1 alone in Keynote 177. Although we are awaiting the formal comparison between nivo/ipi and nivo alone, it is clear reading the trial results that the CTLA-4 is providing meaningful improvements in time to progression and response rates. Conversely there were far fewer patients who were 'primary progressors' compared with PD-1 alone in Keynote 177. I think that it is reasonable to expect improvements in overall survival. We also observed that the toxicity was not very different to PD-1 alone, only requiring 4 doses of low dose ipilimumab. The presented QOL data is further supportive – but ultimately patients in the trial were surviving for longer. Several long term toxicities can occur however – particularly endocrinopathies requiring life long hormone replacement. However most patients and clinicians would accept this for cancer stability. One weakness of the current submission is that it lacks the data of nivo/ipi compared with nivo alone as this data has not yet been presented as it had been yet to reach the required event rate. Given however the substantial improvement compared with pembrolizumab across the trials it is reasonable and necessary to review the submission now as it will benefit UK patients.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Limited to PS 0-1 patients with MSI-H mCRC or unresectable locally advanced colon cancer. There were no sub-groups in Checkmate 8HW who had better outcomes with chemotherapy. Similarly there are no biomarkers to predict clinical complete response. There are a group of patients (mainly with other autoimmune conditions) who would be unable to receive this treatment
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?	There is a higher frequency of dosing with Nivo/ipi (both in induction and maintenance phase – 2wkly, then 4 wkly) than with pembrolizumab (3 wkly, then 6 wkly), both recommended for a 2 year period.

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	However given the improvement in results and patients remaining stable for a longer period this would be justified. This could be discussed with patients upfront. Some smaller centres currently do not deliver combination immunotherapy depending upon local protocols (only PD-1). This is less common than previously given the numerous indications for immunotherapy. There may be an implication that patients cannot receive in their local centre and would need to be referred to a tertiary centre. This situation would need to be explored regionally and again the company could support this.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not currently and would be outside the current evidence base
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
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?	By increasing the chance of complete clinical response there will be an increase in the number of patients who will potentially be cured (or at least have long term survival) with this drug. Unlike many cancer drugs immunotherapy does represent a paradigm change for management of MSI-H mCRC and the combination does appear to provide higher benefits across all endpoints than PD1 alone.

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are specific immune related side effects that are related to this class of drug. These are well described and understood and there are clear management plans for each grade. There can be grade 5 events associated with immunotherapy treatment (eg myocarditis), and thus should only be delivered in specialist centres. Patients are counselled for such a risk – as with any SACT. This risk (with the presented data in mCRC) does not appear higher than with PD-1 alone. This would need to be monitored with RWD post approvals. Of note, in general toxicity rates and QOL scores were improved with Nivo/ipi compared with chemotherapy.
20. Do the clinical trials on the technology reflect current UK clinical practice? • 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?	Yes – upfront MSI-H testing and treatment in 1st line. Same doses as currently utilised MSI testing in keeping with majority of UK testing (some MMR). The requirement for central testing in Checkmate 8HW in my opinion does not alter interpretation and testing in the UK population is performed to a high standard (either in GLH or at a NEQAS approved laboratory) and so I believe these results are translatable to our current UK population. As clinicians we accept the difficulties of seeing an OS signal in this situation given both low event rates and (justifiable) crossover. Therefore PFS rate at 1 and 2 years are critical. Also in this situation in response rates as some patients are able to proceed to surgery when they had been deemed unresectable. Furthermore patients with clinical complete response rates could be cured so this is another important endpoint that rarely achieved in mCRC. We have observed bowel obstructions associated with complete response rarely when primary tumours are in situ (Platt et al, ESMO Open, 2024).

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 since the publication of NICE technology appraisal guidance [TA709]?	No – standard chemotherapy
23. How do data on real-world experience compare with the trial data?	None that I am aware of in the 1st line setting– treatment only recently licensed by EMA. Abstract for 2nd line setting suggest comparable data than trial (https://www.valueinhealthjournal.com/article/S1098-3015(22)04639-3/fulltext)
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 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	No

• 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.	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Immunotherapy has led to paradigm change in the management of MSI-H mCRC of unresectable locally advanced CRC

The combination of nivolimab and ipilimumab has demonstrated high rates of response and long term disease stability which are numerically higher than with single agent PD-1

A higher proportion of patients may be cured when treated with nivolimab and ipilimumab than with PD-1 alone

The toxicity in Checkmate 8HW is comparable to rates with pembrolizumab in Keynote 177

Although the 3rd arm of CheckMate 8HW (nivolimab alone) is not yet reported, given the numerical improvements compared with PD-1 alone, it is important to review this submission now given the benefits to UK patients this treatment could provide.

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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Single Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

Clinical expert statement

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 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.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Wednesday 18 December 2024.** 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, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

Part 1: Treating untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Richard H. Wilson
2. Name of organisation	University of Glasgow
3. Job title or position	
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 untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency? ☒ A specialist in the clinical evidence base for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would 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.	Nil
8. What is the main aim of treatment for untreated unresectable or metastatic colorectal cancer 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)	The main aim of treatment is to prolong overall and progression-free survival by delaying progression of untreated irresectable or metastatic microsatellite instability-high / DNA mismatch repair deficient (hereafter dMMR) colorectal cancer (hereafter mCRC). This will also prolong the disease-control rate (i.e. proportion of those treated who have responding and stable disease), improve symptom control and improve or maintain quality of life. In a subset of patients, disease control (over a period of at least 10 years) is highly likely to equate to cure.
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)	The ideal treatment response to systemic anti-cancer therapy (SACT) we see with nivolumab and ipilimumab (hereafter nivo/ipi) in dMMR mCRC is a complete response where there is no clinical, radiological (and pathological if resection occurs) evidence of locally advanced irresectable tumour or of metastatic disease following treatment. Experience to date has shown us that residual responding or stable disease without a complete response can also have an outcome of no residual active tumour cells and that this can also equate to a potential cure with 10 years free of disease recurrence. This is because residual masses may contain dead tumour cells, necrotic tissue, inflammation and scarring rather than active tumour cells. A partial response or stable disease for a prolonged period of months to years is also very significant with much better outcomes than treatment in these settings of CRC with standard chemotherapies +/- EGFR and VEGF inhibitors where appropriate.

	Given the relative immaturity of the available trial data as regards overall survival (OS) in this setting, the prolonged progression-free survival (PFS) and PFS2 (progression-free survival results of ipilimumab/nivolumab as compared to best standard of care SACT from initiation of first-line therapy to progression on second-line therapy) seen are both extremely clinically significant and augur well for both a clinically and statistically significant OS benefit when this data becomes available with prolonged follow-up.
10. In your view, is there an unmet need for patients and healthcare professionals in untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency?	There are around 44,000 cases of CRC annually in the UK. Of these, ~20% of stage II and ~11% of stage III are dMMR, and a small percentage (<5%) of these are irresectable. Of the ~25% who present with metastatic disease, 3-5% are dMMR. Around 33% with stage II/III dMMR CRC will also progress to metastatic disease despite potentially curative treatment. Hence, there are approximately 1,500 patients with dMMR irresectable or untreated mCRC annually in the UK. Although prognosis with dMMR CRC is better in stage II and III than with proficient DNA mismatch repair (pMMR hereafter) CRC, prognosis is significantly worse with standard care SACT for those with dMMR mCRC than for those with pMMR mCRC. We have thus a significant group of UK patients with significant unmet need every year in the UK. A subgroup of these patients are aged under 50 years old at time of diagnosis, mainly due to germline predisposition from Lynch Syndrome. The clinical trial, cohort and case series data we have seen to date from use of nivo/ipi in dMMR mCRC and irresectable CRC is strongly supportive of significantly improved clinical outcomes in these poor prognosis patients. This includes the potential of dramatically longer 3, 5 and 10 year PFS, cancer specific survival and OS, and ultimately cure in a minority of patients.

11. How is untreated unresectable or metastatic colorectal cancer 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?	In the UK we use the NICE colorectal cancer guidelines (NG151, last updated on 15/12/21). Many oncologists also use the ESMO 2023 guidelines (Cervantes et al, Annals of Oncology) and the US NCCN guidelines (last updated May 2024) but not all the treatment options in either of these latter two documents are available to UK patients with mCRC. Most cancer centres and units in the UK also have local and/or regional guidelines for these patients. The pathway of care in the UK for untreated unresectable or metastatic dMMR CRC is well-defined. Early lines of treatment for mCRC are now very complex with use of single agent and combination therapeutics (cytotoxics, targeted therapies and immunotherapies), de-escalation maintenance strategies, treatment breaks and localised metastasis directed therapies such as surgery, ablation and stereotactic radiotherapy. For unresectable dMMR CRC, we currently use downstaging SACT (combination chemotherapy +/- EGFR inhibitors) and occasionally radiotherapy in an attempt to convert to resectable disease. If possible, resection is performed, but this may leave R1 or R2 (microscopic or macroscopic respectively) residual disease). The prognosis is worse for these patients than for those with R0 (complete) resections. Some patients may be able to access immunotherapy (e.g. pembrolizumab under NICE TAG 709) through local approvals, clinical trials or expanded access schemes. All are then treated on progression using the same guidelines as those with dMMR mCRC. For dMMR mCRC, we routinely use first-line pembrolizumab PD-1 inhibitor monotherapy in all patients (unless this is contra-indicated) following NICE approval. Some patients may access alternate immunotherapy through a clinical trial. If immunotherapy is contra-indicated, we use standard care SACT (chemotherapy +/- EGFR inhibitors).

	Availability of ipi/nivo for untreated unresectable or metastatic dMMR CRC would have a major impact for our current and future patients. The available evidence base to date for dMMR CRC (including the sequential single arm cohort studies in CheckMate 142 and the randomised controlled trial Checkmate 8HW) suggests that the outcomes would be substantially improved with the increased and more durable complete and partial response and stable disease rates and with the improved PFS and PFS2 seen with nivo/ipi compared to monotherapy immune checkpoint inhibition and all other standard care SACT. Important data from the CheckMate 8HW trial has been presented and recently published on the comparison of nivo/ipi versus chemotherapy with or without targeted therapies in untreated dMMR mCRC (Andre et al, N Engl J Med 2024;391:2014-26). At a median follow-up of 31.5 months, PFS outcomes (the primary analysis) were significantly better with nivolumab plus ipilimumab than with chemotherapy (P<0.001); 24 month PFS was 72% with nivolumab plus ipilimumab as compared to 14% with chemotherapy. At 24 months, the restricted mean survival time was 10.6 months longer with nivolumab plus ipilimumab than with chemotherapy. Prespecified subgroup analyses consistently favoured nivolumab plus ipilimumab over chemotherapy, with numerically higher PFS at 12 months in all subgroups, including in patients with baseline RAS or BRAF mutations and baseline liver, lung, or peritoneal metastases. Importantly, this significantly improved efficacy was not at the cost of increased toxicities. In fact, grade 3 or 4 treatment-related adverse events occurred in less (23%) of the patients in the nivolumab plus ipilimumab group than the 48% rate seen in patients in the chemotherapy group. Data for OS in this trial is immature and will not be available in the near future. The comparison between nivo/ipi and nivolumab monotherapy from the CheckMate 8HW trial is not yet available in the public domain but will be presented for the first time (LBA 143) at the GI ASCO meeting on 25th January 2025.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • 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)	The nivo/ipi combination will for most patients replace single agent pembrolizumab in untreated dMMR mCRC. Patients in whom pembrolizumab is contra-indicated will not be able to receive nivo/ipi either for the same reasons. It will replace pembolizumab (where available) and chemotherapy-based SACT in unresectable dMMR CRC unless immunotherapy is contra-indicated. Based on the trial data, nivo/ipi is administered as an out-patient as a combination of nivolumab (240 mg fixed dose) and ipilimumab (1 mg per kilogram of body weight), both administered intravenously on day 1 of a 3 week cycle for 12 weeks, followed by nivolumab (fixed dose of 480 mg) IV as monotherapy on day 1 of a 4 week cycle. Treatment is continued until disease progression, unacceptable toxicities, patient choice to withdraw or for a maximum of 2 years. The usual comparator in current care is pembrolizumab, and this is administered at either 200 mg every 3 weeks or (more often) as 400 mg every 6 weeks as an intravenous infusion over 30 minutes. This is also administered until disease progression, unacceptable toxicities, patient choice to withdraw or for a maximum of 2 years. Hence, there will be more frequent preparation, dispensing and administration of nivo/ipi compared to pembrolizumab, with more frequent patient visits for assessment and treatment, and increased health care resource utilisation. This may be offset as the improved outcomes seen in dMMR CRC with nivo/ipi may reduce longer term resource utilisation as less patients may progress and hence need later line SACT of all types. The long term CheckMate 8HW trial data will allow this to be confirmed or refuted. Other than the above potential change in resource utilisation, there is no significant need for investment in facilities, equipment, or training as the nivo/ipi combination is approved in the UK for use in multiple different cancer types in neoadjuvant, adjuvant and advanced disease settings (albeit with some variation in the doses and schedules used). Nivo/ipi (like all comparator SACT) is usually administered in the UK in secondary care in oncology day hospitals. Treatment is overseen in specialist

	oncology clinics by appropriately trained doctors and non-medical prescribers (i.e. nurses and pharmacists).
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?	Given the trial data available from CheckMate 142 and Checkmate 8HW, and the available real world evidence on use of nivo/ipi in dMMR CRC, I would definitely expect this technology to increase length of life more than our current standard care SACT in many patients. This may also lead to a higher cure rate in patients receiving nivo/ipi but it will take many years for this data to mature and become available. Overall, this clinical benefit will be provided with acceptable levels of SACT induced toxicities as seen in the initial CheckMate 8HW trial data, where higher grade toxicities were seen less often with nivo/ipi than with chemotherapy based treatment. In this trial, better health-related quality of life benefit was also demonstrated through formal testing with validated tools with nivo/ipi as compared with chemotherapy +/- targeted therapy. Such comparative data for the comparison of nivo/ipi versus nivolumab monotherapy will hopefully be available in late January 2025 in the upcoming GI ASCO presentation.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Currently, we have no validated predictive markers for those in whom the technology would be more or less effective i.e. those who will benefit in terms of both prolonged survival and improved/maintained QoL. Often in dMMR mCRC, subgroup analysis from trials and real world evidence shows that patients with tumoural RAS or BRAF mutations or with liver metastases do less well with pembrolizumab or chemotherapy based SACT. This was not seen in the published CheckMate 8HW data for nivo/ipi.

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)	The combination of nivolumab and ipilimumab is one that is frequently used across multiple cancer types in various settings in the NHS and is very familiar to healthcare professionals. Chemotherapy-based SACT for dMMR CRC is usually given every 2 or 3 weeks dependent on regimens used, whereas nivo/ipi is given 3 weekly for the first 12 weeks, then 4 weekly, reducing the frequency of hospital visits. However, duration of treatment with nivo/ipi was significantly longer than with chemotherapy in the CheckMate 8HW trial (median duration of treatment 13.5 months in the nivo/ipi group and 4.0 months in the chemotherapy group. SACT related toxicities (all grade, grade 3 or higher and those leading to discontinuation of any drug in the SACT regimen) are less frequent with nivo/ipi than with chemotherapy. However, some immunotherapy related toxicities can necessitate life-long management e.g. with endocrine replacement therapy.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will start based on standard clinical, radiological, endoscopic and laboratory assessment of patients with untreated unresectable or metastatic dMMR CRC. Treatment will stop on clinical deterioration or radiological progression, on unacceptable toxicities, patient withdrawal of consent or at 2 years maximum duration of treatment. No additional testing other than that typical in the use of immune checkpoint inhibitors in cancer patients will be required.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	Prolonged disease control over many months to years may mean that there is less need for subsequent lines of SACT, for surgery and for radiotherapy

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	reducing drug, hospital admission and other healthcare resource costs. Definitive evidence of this will only come from long term follow up of patients in both trials and in the real world setting.
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?	Based on the evidence available to date from clinical trials and real world data on use of nivo/ipi in dMMR CRC, and from extrapolation from data on use of ipi/nivo in other untreated unresectable or metastatic immunogenic cancers, I firmly believe that this technology will provide a step-change in management of this condition. The improvements in efficacy outcomes seen as compared to current NHS standard of care is highly significant, with major benefit for patients, their carers and families. The particular unmet need of this patient population that is addressed is the improvement in outcomes seen in patients with dMMR CRC as opposed to the results of our best current standard care SACT in patients with pMMR CRC. Previously, our patients with untreated unresectable or metastatic dMMR CRC had significantly worse outcomes than those with untreated unresectable or metastatic pMMR CRC. This has been reversed with the results seen with nivo/ipi in dMMR CRC.
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?	The toxicities of nivo/ipi in patients with cancer of many types including dMMR CRC are well-known and experience and guideline-based care is available in all UK oncology centres and units. Management of these immunotherapy side effects is through dose delay or cessation and use of appropriate supportive medications and procedures.

20. Do the clinical trials on the technology reflect current UK clinical practice? • 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?	There is no reason to believe that the clinical trial results of nivo/ipi in dMMR CRC will not be seen if use of this combination is approved in the UK by NICE. The limited data that we have in the UK on use of nivo/ipi in dMMR CRC through local NHS approvals and in private practice are supportive of this. The most important outcomes were improved complete and partial response and disease control rates, median and landmark (e.g. 12 month and 24 month) progression free survival, and health-related quality of life. The significant outcome that will be measured but that is not currently available due to immaturity of the data is that of overall survival. The surrogate outcome measure of PFS2 is a useful long-term outcome measure, and may be better than PFS at predicting overall survival. These are not adverse effects that were not apparent in clinical trials but have come to light subsequently. The long term nivo/ipi toxicity data (both for common and rare toxities) from clinical trials and real world evidence is available over many years across multiple cancers.
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 since the publication of NICE technology appraisal guidance [TA709]?	No
23. How do data on real-world experience compare with the trial data?	These are very similar from the data that is available, but the CheckMate 8HW phase III randomised controlled trial data is of a much higher quality than that of

	real world data or from the sequential single arm phase II trials in late line moving earlier to first line dMMR mCRC in the CheckMate 142 trials.
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 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.	I do not think that there are any such equalities issues for this treatment and condition.

Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Nivolumab/ipilimumab results in improved progression-free survival compared to current NHS standard care SACT in untreated unresectable or metastatic dMMR CRC.
Nivolumab/ipilimumab has less SACT related adverse events than current NHS standard care chemotherapy based SACT in untreated unresectable or metastatic dMMR CRC.
Nivolumab/ipilimumab has been shown to provide better health-related quality of life than current NHS standard care chemotherapy based SACT in untreated unresectable or metastatic dMMR CRC.
Nivolumab/ipilimumab is likely to result in improved overall survival compared to current NHS standard care SACT in untreated unresectable or metastatic dMMR CRC.
Nivolumab/ipilimumab is likely to result in an increased cure rate compared to current NHS standard care SACT in untreated unresectable or metastatic dMMR CRC.

Thank you for your time.

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The information that you provide on this form will be used to contact you about the topic above.

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Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]:

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Author contributions

Maxwell S. Barnish	Project manager. Led the review of the clinical effectiveness evidence. Contributed to writing and editing the report.
Jemma Perks	Critical appraisal of the company's statistical analysis. Contributed to writing and editing the report.
Ahmed Abdelsabour	Critical appraisal of the company's economic evidence, conducted additional economic analysis, and contributed to sections of the report.
Alan Lovell	Critical appraisal of the company's literature search strategies. Contributed to writing and editing the report.
G.J. Melendez-Torres	Critical appraisal of the company's statistical analysis
Ian Fraser	Clinical expert. Provided clinical expert input for the development of the report in two phone calls.
Dawn Lee	Project director and lead health economist. Led the review of the cost effectiveness evidence. Led production of EAG model analyses. Contributed to writing and editing the report.

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Table of abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
AE	Adverse event
AIC	Academic in confidence
AIC	Akaike information criterion
BIC	Bayesian information criterion
BICR	Blinded independent committee review
BMS	Bristol-Myers-Squibb
BOR	Best overall response
BSC	Best supportive care
CAPOX	Capecitabine and oxaliplatin
CI	Confidence interval
CIC	Commercial in confidence
CM	CheckMate
CQ	Clarification question
CR	Complete response
CRC	Colorectal cancer
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DIC	Deviance information criterion
dMMR	Deficient DNA mismatch repair
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	EuroQoL 5 Dimensions
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life questionnaire
ESS	Effective sample size

Abbreviation	Definition
FDA	Food and Drug Administration
FOLFIRI	Folinic acid, fluorouracil, and irinotecan hydrochloride
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin
FOLFOXIRI	Folinic acid, fluorouracil, oxaliplatin and irinotecan
FP	Fractional polynomial
HR	Hazard ratio
HRQoL	Health-related quality of life
HSE	Health Survey England
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IHC	Immunohistochemistry
Inc	Incremental
IO	Immuno-oncology
IPI	Ipilimumab
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan Meier
KN	KEYNOTE
LY	Life years
LYG	Life years gained
MA	Marketing authorisation
MAIC	Matching-Adjusted Indirect Comparison
mCRC	Metastatic colorectal cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability high
MSS	Microsatellite stable
NA	Not available
NG	NICE Guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIVO	Nivolumab

Abbreviation	Definition
NMA	Network meta-analysis
NR	Not reached
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
PCR	Polymerase chain reaction
PD-L1	Programmed death ligand 1
PEMBRO	Pembrolizumab
PenTAG	Peninsula Technology Assessment Group
PF	Progression-free
PFS	Progression-free survival
pMMR	Proficient mismatch repair
PPS	Post-progression survival
PR	Partial response
PrePS	Pre-progression survival (PF to death transition)
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
QA	Quality assessment
QALY	Quality-adjusted life year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RMST	Restricted mean survival time
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of care
TA	Technology appraisal
TRAE	Treatment-related adverse event

Abbreviation	Definition
TTD	Time-to-discontinuation
TTP	Time-to-progression
UK	United Kingdom

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. 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 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

Broadly speaking the key clinical issues related to the lack of overall survival data and issues with the transitivity of the NMA network. In terms of cost effectiveness issues, the key issues related to the modelling of post-progression survival and subsequent treatments, the assumption that gains experienced in PFS will directly translate to gains in OS and related issues in the validation of OS and long-term assumptions for TTP, the modelling of time on treatment and the costs used for disease management.

Table 1: Summary of key issues

ID	Summary of issue	Report sections
#1	Lack of OS data from CM8HW	3.2.3.1
#2	Transitivity of NMA network	3.4
#3	Post progression survival and subsequent treatments	4.2.2.4, 4.2.6.4 and 4.2.8.2
#4	Uncertainty in the treatment effect	4.2.2.1, 4.2.6.1 and 4.2.6.5
#5	Time on treatment	4.2.2.2 and 4.2.6.6
#6	Cost of disease management	4.2.8.3

Abbreviations: NMA, network meta-analysis; OS, overall survival

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Time on treatment	Time on treatment for PEMBRO and NIVO + IPI is assumed to be the same	Time on treatment for PEMBRO is assumed to be lower than time on treatment with NIVO + IPI based on the HR applied to TTP	4.2.6.6 and 6.2.5
Subsequent treatments	All patients getting subsequent treatment receive NIVO + IPI in chemotherapy arm and FOLFOX in the PEMBRO and NIVO + IPI arms	Use trial data to inform the subsequent treatments used and 42% get PEMBRO rather than NIVO + IPI after chemotherapy based on data from Peter Clark, the NHS Cancer Drugs Fund lead	4.2.2.4, 4.2.8.2 and 6.2.3
Post progression survival	PPS is the same for all treatments regardless of the subsequent treatment received	PPS for patients after chemotherapy taken from exponential fit to CM142 OS to reflect expectation of improved survival with NIVO + IPI	4.2.6.4 and 6.2.1
Treatment effect on TTP	Size of treatment effect for NIVO + IPI vs PEMBRO increases infinitely	Hazards for PEMBRO and NIVO + IPI set equal at 2 years	4.2.6.1, 4.2.6.3 and 6.2.8
Subsequent treatment costs	Per cycle cost based upon mean cycles spent in progression taken from RMST analysis of CM142 NIVO + IPI data (unclear which cohorts) applied to the number of cycles spent in progressive disease in the model creating a mismatch in data sources	Subsequent treatment costs applied using payoff approach	4.2.8.2 and 6.2.2
Resource use	2 weekly oncologist consultations continue for the entire time a patient is progression-free, there is the same frequency for all treatments and BSC costs from a source – which relates only to costs for the last 6 months of life from Finland – apply for the entire time spent post-progression regardless of whether or not active treatment is received	Oncologist visits align with treatment administration visits and once patients are off treatment taper off and stop when patients are discharged at 5 years. Resource use costs for 2nd line treatment align with those for 1L treatment. Palliative care costs only align to patients receiving palliative care in line with UK practice.	4.2.8.3 and 6.2.9
Population weight	Use trial body weight ([redacted]) to calculate wastage	Use HSE data to calculate wastage	4.2.3 and 6.2.10

	Company's preferred assumption	EAG preferred assumption	Report Sections
Chemotherapy comparator	Market shares from Clinical Advisory Board	Use trial data for the split of treatments included in the chemotherapy comparator	4.2.4 and 6.2.11
Population weight	Use trial body weight ([redacted]) to calculate wastage	Use HSE data to calculate wastage	4.2.3 and 6.2.10
Half-cycle correction	Half-cycle correction for TTD	No half-cycle correction for TTD	4.2.2.5

Abbreviations: 1L, first line; BSC, best supportive care; EAG, External Assessment Group; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; HSE, Health Survey England; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; PPS, post-progression survival; RMST, restricted mean survival time; TTD, time-to-discontinuation; TTP, time-to-progression; UK, United Kingdom; CM, CheckMate

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology was modelled to affect QALYs by:

- Increasing pre-progression survival which is assumed to directly translate to gains in OS
- Increased quality of life in the progression-free state relative to chemotherapy

Overall, the technology was modelled to affect costs by:

- Increasing drug costs
- Reducing subsequent treatment costs relative to chemotherapy (where NIVO + IPI and PEMBRO can be used at 2nd line)
- Increasing administration costs relative to PEMBRO and reducing administration costs relative to chemotherapy
- Increasing resource use in the progression-free state
- Reducing the costs associated with best supportive care which is applied for the entire duration of the progressed state

The modelling assumptions that had the greatest effect on the ICER were

- Whether an OS benefit is assumed versus PEMBRO or not
- The modelling of post-progression survival (PPS) and subsequent treatment costs and quality-of life impact
- How PEMBRO time on treatment is calculated

Most EAG scenarios maintained a relatively high ICER against chemotherapy at list price, suggesting that the cost effectiveness of NIVO + IPI versus chemotherapy remains sensitive for changes in the modelling assumptions.

Scenario analysis using a shorter time horizon showed that much of the benefit versus chemotherapy is accrued beyond 5 years (the limit of trial data), both in incremental QALYs and in build-up of costs (particularly BSC costs post-progression).

1.3. The decision problem: summary of the EAG's key issues

The EAG did not identify any key issues related to the decision problem.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified two key issues related to the clinical effectiveness evidence – the lack of OS data and issues with the transitivity of the NMA network.

Key Issue 1: Lack of OS data from CM8HW

Report sections	3.2.3.1
Description of issue and why the EAG has identified it as important	OS data from CM8HW were not presented in the CS. OS is the endpoint listed first on the NICE scope and is important to inform / validate the economic model. The company said that OS data for the pivotal trial were not provided yet to the company by their vendor as the pre-specified number of events had not been reached. (clarification response A21). In the clarification question, the EAG stated that it was aware that the data would not be mature and would be treated as such, but that provision of these data was essential to enable appropriate model validation. The EAG noted that at the time of the interim analysis (12 October 2023), the information fraction was 80%, suggesting that OS data at this point in time would likely closely parallel the final OS data. The company justified its position based on the hierarchical statistical testing strategy pre-specified in the trial protocol and to "preserve the trial's integrity and to avoid introducing bias that could potentially lead to inaccurate conclusions".

Report sections	3.2.3.1
	The EAG also noted that death data is available (as this is a safety endpoint) and that in 3 of the 5 example TAs quoted by the company OS data was supplied before the Committee made a decision; the remaining two were in the adjuvant space where surrogacy between DFS and OS can be considered more intuitive given the potentially curative nature of surgery. The EAG considered that the production of an ad hoc confidential analysis for regulatory and decision-making purposes would be standard and that the company's decision not to do this is a major issue for the appraisal. The surrogacy of OS, as determined by PFS, is based on the post-hoc correlation between PFS and OS from cohort 3 (1L NIVO + IPI) in the CM142 trial (n=45, median follow-up 52.6 months). This analysis did not demonstrate that the model assumption that gains in TTP will directly translate to gains in OS is reasonable. Overall, conclusions regarding OS have very limited interpretability, and the EAG were limited in the appraisal of its surrogacy. The EAG noted that there were 44 deaths on the NIVO + IPI arm (22%) and 37 deaths on the chemotherapy arm (42%); whilst these data are immature there is enough information available to be able to provide some validation. The initial datacut of KN-177 had 56 deaths in the PEMBRO arm (37%) versus 69 in the chemotherapy arm (45%) indicating that there may be some advantage in OS for NIVO + IPI. However, without KM data this information was difficult to interpret.
What alternative approach has the EAG suggested?	Provision of an ad hoc analysis confidentially, which could be an analysis that has been submitted to MHRA, EMA or FDA.
What is the expected effect on the cost-effectiveness estimates?	The absence of OS data from the pivotal trial increases uncertainty in the cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Analysis of OS data.

Abbreviations: 1L, first line; CM, CheckMate; CS, company submission; DFS, disease-free survival; EAG, External Assessment Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; IPI, ipilimumab; KM, Kaplan Meier; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival.

Key Issue 2: Transitivity of NMA network

Report sections	3.4
Description of issue and why the EAG has identified it as important	Transitivity of the network relies on the generalisability of centrally vs. locally tested microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) status between the trials. In KN-177, dMMR/ MSI-H status is locally confirmed and therefore it is appropriate to compare all randomised patients in the ITC. Nevertheless, the EAG considered the use of central testing important for preventing non-differential ascertainment bias.

Report sections	3.4
	Unfortunately, central testing was not performed in KN-177, which prevents a robust like for like comparison from being carried out. Furthermore, transitivity of the network relies on the class treatment effect, resulting from the control arms. The EAG noted that the heterogeneity within the comparator groups adds a level of uncertainty to the estimate. The company presented evidence that, within the chemotherapy arms of CM8HW and KN-177, they are similar enough for comparison. Yet some heterogeneity in outcomes may be explained by the percentage of patients receiving bevacizumab (CM8HW = 64% vs. KN-177 = 70%), which is not used in UK practice. This added a level of uncertainty to the estimates produced by the FP NMA.
What alternative approach has the EAG suggested?	The EAG was unable to suggest an alternative approach. The ITC used the ITT (all randomised patients' population) as expected. Conclusions were drawn to reflect this as opposed to the centrally confirmed population/ primary end point.
What is the expected effect on the cost-effectiveness estimates?	Increases uncertainty in the cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	The EAG noted that there is no such evidence available as there is no possibility of central testing in the KN-177 cohort. This issue relates to an unresolvable uncertainty.

Abbreviations: CM, CheckMate; dMMR, DNA deficient mismatch repair EAG, External Assessment Group; FP, fractional polynomial; ITC, Indirect treatment comparison; ITT, intention to treat; KN, KEYNOTE; MSI-H, microsatellite instability high; NMA, network meta-analysis;

1.5. The cost effectiveness evidence: summary of the EAG's key issues

Key Issue 3: Post progression survival and subsequent treatments

Report sections	4.2.2.4, 4.2.6.4 and 4.2.8.2
Description of issue and why the EAG has identified it as important	The model made several assumptions around subsequent treatment types and effectiveness which did not align with expectations: • Data from an advisory board were used to model subsequent therapy type divorcing costs and effectiveness • Only NIVO + IPI was used after chemotherapy – this did not align with data from Peter Clark that ~35 vs ~25 patients receive NIVO + IPI and PEMBRO in this setting; additionally, some patients may receive standard chemotherapy • NIVO + IPI was no more effective as a subsequent treatment than standard chemotherapy – this did not align with the company's own model in TA716 • NIVO + IPI and PEMBRO were both given for a full 2 years as subsequent treatments – this did not align with data from CM8HW where patients received less than 2 years of treatment on average and would not be expected to receive a full 2 years of treatment despite the lack of a stopping rule for NIVO + IPI for previously treated patients

Report sections	4.2.2.4, 4.2.6.4 and 4.2.8.2
	• No patients received encorafenib with cetuximab as a subsequent treatment, despite this being a standard treatment used in UK practice • The scenario supplied by the company using OS data for Cohort 2 to model outcomes for subsequent NIVO + IPI used an exponential fit with no justification for this provided In addition, there was a minor error in the way the calculations were conducted to apply subsequent treatment costs.
What alternative approach has the EAG suggested?	The EAG corrected the error in the application of subsequent treatment costs and assumed (in the absence of data from Cohort 2 in CM142) a mean time on treatment for NIVO + IPI and PEMBRO in the 2nd line of [redacted] based on the mean time on treatment in CM8HW. This was likely to somewhat overestimate the duration at 2nd line. The EAG considered that subsequent NIVO + IPI and PEMBRO are more effective than subsequent chemotherapy and that this should be reflected in transition probabilities as well as costs. The EAG explored several scenarios around subsequent treatment use and post progression survival, including: • Use of subsequent treatment data per the trials • Use of subsequent IO use data supplied by Peter Clark • Inclusion of encorafenib with cetuximab as a subsequent treatment • Use of company supplied scenario analysis for NIVO + IPI PPS outcomes • PPS for chemotherapy based upon difference in life years from TA716 • Reduced PPS for subsequent PEMBRO vs subsequent NIVO + IPI • Equal PPS to TA709 for PEMBRO and NIVO + IPI • Increased quality of life for patients receiving IOs as a subsequent therapy rather than chemotherapy
What is the expected effect on the cost-effectiveness estimates?	Use of subsequent treatment data from the trials increased the list-price ICER by over [redacted] versus chemotherapy; there was limited impact in the comparison to PEMBRO. Using the data on IO split from Peter Clark had limited impact on top of this at list-price. Inclusion of encorafenib with cetuximab costs had limited impact. Use of CM142 for subsequent NIVO + IPI after chemotherapy reduced the QALYs gained versus chemotherapy from [redacted] to [redacted] Using CM142 data and reducing the effectiveness of PEMBRO as a subsequent treatment increased the incremental QALYs back up to [redacted] Assuming equal PPS to TA709 for PEMBRO and NIVO + IPI on top of CM142 for subsequent NIVO + IPI after chemotherapy reduced the QALYs gained versus chemotherapy to [redacted] This scenario is likely to be more reflective of the pathway post NIVO + IPI in practice as IOs were not available for previously treated patients when KN-177 was conducted. The scenario of improved utilities for patients undergoing chemotherapy in PPS also has a substantial impact when

Report sections	4.2.2.4, 4.2.6.4 and 4.2.8.2
	applied on top of the EAG-base case reducing the incremental QALYs versus chemotherapy from [redacted] to [redacted]
,What additional evidence or analyses might help to resolve this key issue?	The company could provide the mean duration of treatment for CM142 Cohort 2 and parametric curve fits to OS data from Cohort 2.

Abbreviations: CM, CheckMate; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; IO, immuno-oncology; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PEMBRO, pembrolizumab; PPS, post-progression survival; QALY, quality-adjusted life year

Key Issue 4: Uncertainty in the treatment effect

Report sections	4.2.2.1, 4.2.6.1 and 4.2.6.5
Description of issue and why the EAG has identified it as important	The model assumed that gains experienced in PFS would directly translate to gains in OS; this was particularly uncertain in the comparison to PEMBRO. As NIVO monotherapy and OS data for all arms were not provided from CM8HW the EAG was unable to validate this assumption in any meaningful way. There was uncertainty around the most appropriate curve fit for TTP. The company selected the individual curve fits of the generalised gamma curve for NIVO + IPI and chemotherapy on the basis of it having the lowest AIC for NIVO + IPI, input from an advisory board (details not provided), consideration that the extrapolation validated reasonably well against TTP from CM142, PFS from KN-177 using landmark survival and restricted mean survival time, and limited comparison with other published literature sources. However, the curve did not fit well to the observed data. Spline models supplied by the company in clarification responses provided a better fit to observed data and equally plausible long-term estimates. The model assumed the treatment effect on TTP applied over a lifetime horizon. In the comparison to PEMBRO, due to the form of the FP NMA chosen, this resulted in a hazard ratio remains below 1 for the entire modelled time horizon and a survivor function than continues to diverge, albeit at a slower rate, in the long-term when clinical expectation is that any gains versus PEMBRO would be observed within the first year or two. Validation exercises found that: • The model underpredicted outcomes for PEMBRO in the long-term when compared to PD-1/PD-L1 monotherapy data for PFS and OS • The model overpredicted outcomes for NIVO + IPI in the long-term when compared to CM142 data. This was surprising, given patients in CM142 may be expected to have a better prognosis than those in CM8HW given that reinitiation was allowed • 60% of patients were predicted to be long-term survivors (% remaining alive at 10 years) on the NIVO + IPI arm. This compared to a BICR-assessed CR rate of only [redacted] The model did not allow the use of the FP NMA to model outcomes for NIVO + IPI, despite requests for this functionality from the EAG on

Report sections	4.2.2.1, 4.2.6.1 and 4.2.6.5
	the clarification call. This meant that outcomes were modelled using a different framework for PEMBRO and NIVO + IPI, which is not ideal.
What alternative approach has the EAG suggested?	The EAG presented scenario analysis assuming equal OS between NIVO + IPI and PEMBRO which, without alternative data being presented, the EAG considered to be as plausible as the EAG base case. The EAG considered the spline model equally appropriate to model TTP and presented scenarios around treatment effect waning aimed at ensuring a more plausible long-term treatment effect.
What is the expected effect on the cost-effectiveness estimates?	Assuming equal OS, the list-price ICER for NIVO + IPI vs PEMBRO was [redacted] Using the two-knot spline model reduced the list-price ICER by [redacted] in the comparison to PEMBRO and [redacted] in the comparison to chemotherapy. Assuming that the hazards were equal for NIVO + IPI and PEMBRO from 2 years onwards increased the list-price ICER by [redacted] in the comparison to PEMBRO.
What additional evidence or analyses might help to resolve this key issue?	Provide OS data for NIVO + IPI and chemotherapy Provide NIVO mono data to give reassurance on benefits vs PEMBRO. Provide functionality to implement the FP NMA for NIVO + IPI as well as PEMBRO in the model. Provide data on the number of patients reinitiating in CM142 and the impact of this on outcomes.

Abbreviations: AIC, Akaike Information Criterion; BICR, Blinded independent committee review; CM, CheckMate; CR, complete response; EAG, External Assessment Group; FP, fractional polynomial; IPI, ipilimumab; KN, KEYNOTE; NIVO, nivolumab; NMA; network meta-analysis; OS, overall survival; PD-L1, programmed death ligand 1; PEMBRO, pembrolizumab; PFS, progression-free survival; TTP, time-to-progression;

Key Issue 5: Time on treatment

Report sections	4.2.2.2 and 4.2.6.6
Description of issue and why the EAG has identified it as important	The company assumed that time on treatment for PEMBRO and NIVO + IPI were equal, despite PEMBRO having a faster time to progression. This was based on a naïve comparison of time on treatment between trials that failed to account for differences in the outcomes reported in the chemotherapy arm.
What alternative approach has the EAG suggested?	The EAG considered that time on treatment for PEMBRO should be lower than for NIVO + IPI and therefore we applied the HR from the NMA to TTP to the curve fit for NIVO + IPI to TTD to provide a more reasonable estimate of relative time on treatment.
What is the expected effect on the cost-effectiveness estimates?	When TTD for PEMBRO was assumed to be reduced by the same amount as TTP relative to NIVO + IPI the list-price ICER versus PEMBRO increased by over [redacted]
What additional evidence or analyses might help to resolve this key issue?	TTD Kaplan Meier data from KN-177. The EAG acknowledged the company does not have access to this.

Abbreviations: CM, CheckMate; EAG, External Assessment Group; HR, hazard ratio; IPI, ipilimumab; KM, Kaplan Meier; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab; TTD, time-to-discontinuation

Key Issue 6: Cost of disease management

Report sections	4.2.8.3
Description of issue and why the EAG has identified it as important	Resource use costs were highly inconsistent across previous appraisals. The costs used in this appraisal appear to lack face validity in a number of areas: • Visits with a consultant were assumed to occur once every 2 weeks on top of drug administration for the entire patient's lifetime whilst progression free • Palliative care costs applied to the entire time following progression, even when patients are on a 2L treatment (the cost applied is £1,623 per month; the source this comes from is an article from Finland which looks at palliative care costs in the last 6 months of life in 2010)
What alternative approach has the EAG suggested?	The EAG preferred to use the estimates supplied by our clinical expert which accounted for clinical practice. These estimates assumed that: • Oncologist visits align with treatment administration visits and once patients are off treatment taper off and stop when patients are discharged at 5 years. • Resource use costs for 2nd line treatment align with those for 1st line treatment. • Palliative care costs only align to patients receiving palliative care in line with UK practice.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of NIVO + IPI relative to PEMBRO and chemotherapy improves due to a substantial reduction in costs within the PF health state which offsets the loss of benefit from inflated costs in the PD state.
What additional evidence or analyses might help to resolve this key issue?	Additional validation of the appropriateness of resource use assumptions with clinical experts; or a more relevant UK source for costs.

Abbreviations: 2L, second line; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; UK, United Kingdom

1.6. Other key issues: summary of the EAG's views

The EAG did not identify any other key issues, not covered by the sections above.

1.7. Summary of EAG's preferred assumptions and resulting ICER

Modelling errors identified and corrected by the EAG are described in Section 6 along with the EAG's preferred modelling assumptions and exploratory scenario analysis conducted by the EAG. The impact of modelling errors on the ICER was low. The modelling assumptions that had the greatest effect on the ICER were:

- Whether an OS benefit is assumed versus PEMBRO or not (scenario analysis ICER [redacted]
- The modelling of post-progression survival (PPS) and subsequent treatment costs and quality-of life impact
- How PEMBRO time on treatment is calculated

Table 3: EAG's preferred model assumptions (list-price)

Preferred assumption	Section in EAG report	Inc costs vs PEMBRO	Inc QALYs vs PEMBRO	Inc costs vs Chemo	Inc QALYs vs Chemo	ICER £/QALY vs PEMBRO	ICER £/QALY vs Chemo	+/- company base case vs PEMBRO	+/- company base case vs Chemo
EAG corrected company base case	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use HSE data to calculate wastage	6.2.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No half-cycle correction for TTD	6.2.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use trial data for the split of treatments included in the chemotherapy comparator	6.2.11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use trial data to inform the subsequent treatments used	6.2.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS for patients after chemotherapy taken from exponential fit to OS from CM142	6.2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42% get PEMBRO rather than NIVO + IPI after chemotherapy based on data from Peter Clark	6.2.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs applied using payoff approach	6.2.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO TTD calculated by applying TTP HR to NIVO + IPI TTD curve	6.2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards for PEMBRO and NIVO + IPI set equal at 2 years	6.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use based on EAG clinical expert input	6.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of EAG base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; HSE, Health Survey England; TTD, Time-to-discontinuation; Inc, incremental; Chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALY, quality adjusted life-years; PPS post-progression survival; CM, CheckMate; TTP, time-to-progression; HR, hazard ratios

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by Bristol-Myers-Squibb (BMS) in support of nivolumab with ipilimumab for treating previously untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.

2.2. Critique of the company's description of the underlying health problem

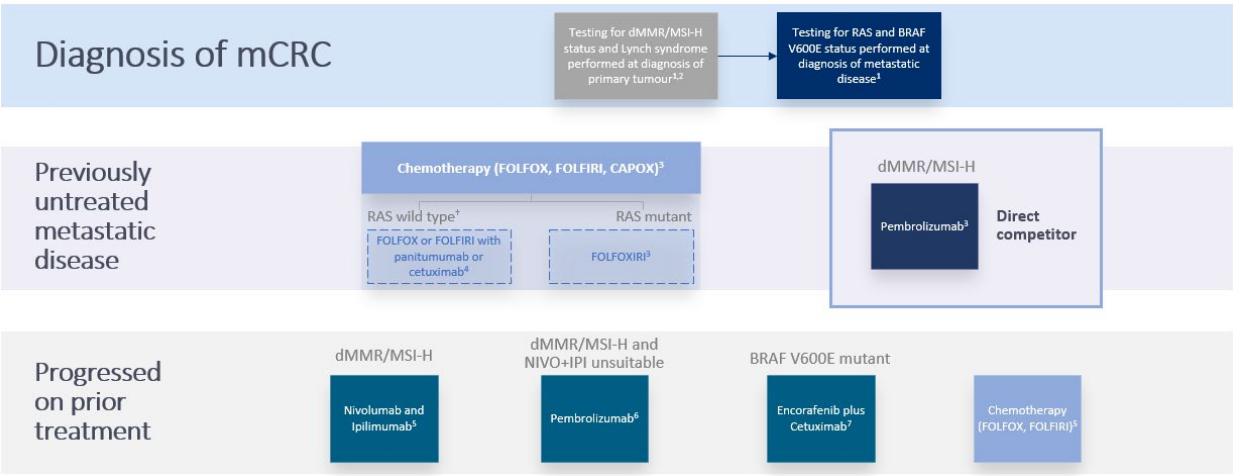
The company's description of the underlying health problem, unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency, is summarised in the CS Document B Section 1.3. Colorectal cancer (CRC) is a malignant tumour arising from the linings of the colon and rectum. CRC is the third most common cancer internationally[1] and the fourth most common cancer in the UK, responsible for 34,405 new cases in England in 2020.[2] CRC is the second most common cause of cancer mortality in the UK, accounting for 10% of cancer deaths (n=14,033) in 2020.[2] CRC is strongly age-associated, with more than 90% of new cases in those over 50 and the highest incidence being in those aged 70-79,[2] although the incidence in under 50s is rising.[3] CRC is generally considered advanced when the tumour has spread into tissues around the bowel or nearby lymph nodes (locally advanced) or metastatic CRC (mCRC), which is when disease has spread beyond the large intestine and nearby lymph nodes.[4] Mismatch repair deficiency (dMMR) CRC is a discrete molecular subtype, accounting for 4-5% of mCRC tumours.[5,6] It is characterised by an inability to repair certain classes of spontaneous mutations within repetitive DNA sequences or microsatellites, generally resulting in high microsatellite instability (MSI-H).[7-9] dMMR and MSI-H have a low discordance rate (1.6%-3.4%),[10-12] meaning that it is generally not necessary to test for both.[13] Clinical advice to the EAG was that the company's description of the underlying health problem is accurate and that the key prognostic factors in this population are performance status, age (partly due to comorbidity burden), disease burden (such as liver metastases) and molecular factors. Patients with BRAF mutation tend to have the worst prognosis.

2.3. Critique of the company's overview of current service provision

The company's current care pathway is described in the CS Document B Section 1.3.2.

Additionally, in Section B.1.3.1.2, the company cites NICE guidelines recommending testing for dMMR/MSI-H status in all cases of CRC.[14] The company's treatment pathway was based on NICE guideline NG151, diagnostics guidance DG27, and technology appraisals TA709, TA439, TA668, TA716, and TA914. The company's treatment pathway is shown below as Figure 1.

Figure 1: Company's treatment pathway for metastatic colorectal cancer.



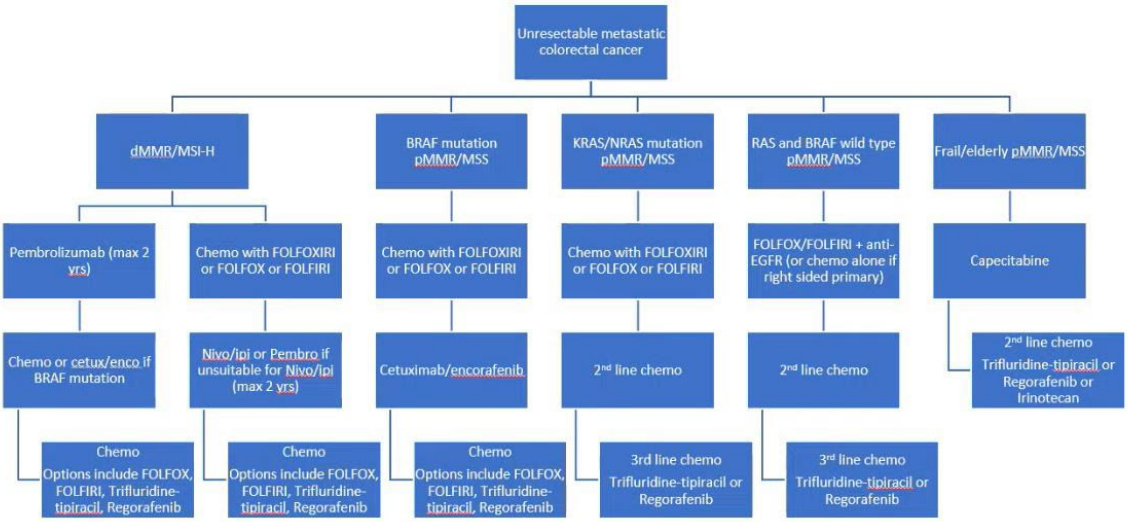
Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficiency; EGFR, epidermal growth factor receptor; MSI-H, microsatellite instability high

Note: † Cetuximab is only an option for epidermal growth factor receptor (EGRF) expressing tumours

Sources: 1) NICE NG151. 2) NICE DG27 3) NICE TA709 4) NICE TA439 5) NICE TA716 6) NICE TA914 7) NICE TA668.

Clinical advice to the EAG was that treatment options in CRC have become increasingly complex, depending on test results that come back from the regional genomics hub. Patients with dMMR/MSI-H CRC would receive a checkpoint inhibitor (immunotherapy with pembrolizumab) at first line, or if not possible (e.g. result not ready in time or chemotherapy preferred for a rapid response), then double or triplet chemotherapy at first line with immunotherapy at second line. The treatment algorithm the EAG received in clinical advice is shown in Figure 2, noting this may reflect local treatment preferences. Both treatment pathways identify PEMBRO as a key comparator in the dMMR/MSI-H group. In the dMMR/MSI-H group, the choice at first line would typically be between PEMBRO or one of the chemotherapy regimens (FOLFOXIRI, FOLFOX and FOLFIRI). The EAG noted that the company model did not include cetuximab with encorafenib as a subsequent treatment option.

Figure 2: Metastatic colorectal cancer treatment algorithm from EAG's clinical advisor



Source: clinical advisor to the EAG

The introduction of NIVO + IPI into the treatment pathway is likely to lead to some displacement of PEMBRO and existing chemotherapy regimens. However, clinical advice to the EAG was that this is not likely to result in any fundamental re-organisation of service provision.

The intervention for this appraisal is a combination therapy – nivolumab (NIVO) with ipilimumab (IPI). NIVO is a human IgG4 monoclonal antibody, which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2.[15] IPI is a human IgG1κ monoclonal antibody. It is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway.[16] It is anticipated that NIVO + IPI will be indicated for the 1L treatment of adult patients, 18 years and older, with unresectable or metastatic dMMR/MSI-H CRC. [redacted] The company's proposed dosing for adult patients is NIVO 240 mg + IPI 1 mg/kg IV Q3W for 4 doses then NIVO 240 mg IV Q2W or 480 mg IV Q4W. Both NIVO and IPI are given by intravenous administration. The company's position is that no additional tests are required as testing is currently routinely conducted as recommended by NICE guidelines.

2.4. Critique of company's definition of decision problem

The company submission (CS) covers the full anticipated marketing authorisation for NIVO + IPI. The EAG presents its critique of the decision problem below in Table 4. The EAG considered the company decision problem to be fairly well aligned to the NICE scope.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People aged 12 years and older with previously untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatched repair deficiency.	As per NICE scope. It is noted that the company revised its intended population to be adults 18 and over, following a change in the expected marketing authorisation (MA).	The narrowing of the population was to reflect the expected MA. The scope was not revised, as the appraisal had already commenced.	The company decision problem aligned with the NICE scope. The EAG report focuses on the adult population, following advice from NICE that the company's intended MA had been revised to only include adults aged 18 and over.
Intervention	Nivolumab + ipilimumab (NIVO + IPI)	As per NICE scope	NA	The EAG was satisfied that the intervention described in the CS matched the intervention described in the final scope. The technology is NIVO + IPI. The proposed marketing authorisation is for 1L treatment of adults, with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).
Comparator(s)	For all people: • Pembrolizumab (PEMBRO) • Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI)	As per NICE scope	NA	The EAG considered that the list of comparators was appropriate and matched the final scope. The EAG considered PEMBRO to be likely the key comparator. Clinical advice is that NIVO and PEMBRO can generally be seen as interchangeable, although local procedures may stipulate which shall be considered the default. In response to clarification (A6), the company confirmed FOLFOXIRI was accounted for as a comparator in this submission.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Capecitabine plus oxaliplatin (CAPOX) • Capecitabine For people with RAS mutant mCRC: • Folinic acid plus fluorouracil plus oxaliplatin plus irinotecan (FOLFOXIRI) For people with RAS wild type mCRC: • Panitumumab in combination with FOLFOX or FOLFIRI For people with EGFR expressing, RAS wild-type mCRC: Cetuximab in combination with FOLFOX or FOLFIRI			
Outcomes	• OS • PFS • Response rates • AEs of treatment • QoL	As per NICE scope.	NA	The EAG considered that the outcomes in the company decision problem are well aligned to the NICE scope and capture all the key outcomes. However, it was noted that while OS was in the company's decision problem and was collected in the trials, no OS data were presented in the CS for the pivotal RCT. Response rate data for

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				CM8HW were also not presented in the CS as these were a secondary outcome not assessed in the interim trial analysis. In the absence of OS data, the EAG considered it important to assess available data for time to next treatment (TTNT)
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 Personal Social Services perspective. The availability and cost of biosimilar and generic products should be taken into account. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per NICE scope.	NA	The EAG considered the company's economic analysis to be reasonably well aligned to the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Subgroups	If evidence allows, subgroups based on RAS mutation status will be considered.	• BRAF/KRAS/NRAS mutation status (efficacy data reported) • Patients treated without bevacizumab (efficacy data reported)	• In the CM8HW subgroup analysis, the HR for progression in the KRAS-mutant subgroup (n=45) was similar to the HR (95% CI) for the whole centrally confirmed population (0.24 [0.09, 0.63] vs. 0.20 [0.14, 0.31]). KRAS mutation appears to have no significant impact on the comparative efficacy of NIVO + IPI. • Subgroup analysis for bevacizumab was conducted because it is no longer recommended by NICE in this indication	The EAG considered that the subgroup by mutation status was in line with the NICE scope, while the subgroup without bevacizumab is in addition to the scope. The EAG considered that a subgroup analysis without patients treated using bevacizumab makes *a priori* sense given it is no longer recommended by NICE and as such shall not be considered part of standard care. The EAG considered the economic subgroup analysis presented to be fundamentally flawed in that they failed to account for potential differences in baseline risk.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Special considerations including issues related to equity or equality	NA	No equality issues have been identified or are anticipated	NA	Clinical advice to the EAG indicated that age and geographical location could be important equity considerations. Older patients on average have worse prognosis and treatment response. The EAG was advised that, for example in rural areas of Devon and Cornwall, people may have to travel over an hour to access hospital appointments, even if they have access to a car. This situation may be reflected in other rural areas across the country.

Abbreviations 1L, first line; AE, adverse event; CAPOX, capecitabine plus oxaliplatin; CI, confidence interval; CRC, colorectal cancer; CS, company submission; dMMR, deficient DNA mismatch repair; EAG, External Assessment Group; EGFR, epidermal growth factor receptor; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, fluorouracil (5FU), oxaliplatin and irinotecan; HR, hazard ratio; IPI, ipilimumab; NA, not applicable; NHS, National Health Service, MA, marketing authorisation; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability high; NICE, National Institute for Health and Care Excellence; NIVO, nivolumab; PFS, progression-free survival; QALY, quality adjusted life year; QoL, quality of life; OS, overall survival; PEMBRO, pembrolizumab; TTNT, time to next treatment.

3. CLINICAL EFFECTIVENESS

The EAG identified two key issues in the clinical effectiveness evidence:1) lack of OS data from CM8HW and 2) issues with transitivity in the NMA.

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to assess the clinical effectiveness (efficacy and safety) of first-line interventions for recurrent or metastatic CRC.

Table 5: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	B.2.1, Appendix D	The company searched a reasonable range of databases for the clinical SLR, used a suitable set of keywords and thesaurus terms for the population and intervention, and transparently reported the (adapted) study type filters used. There was a small reporting error in CS Document B as the population searched for in the search strategy (Appendix D) was the dMMR/MSI-H population. However, Document B stated that the search was for a different population: "1L treatment of recurrent or metastatic CRC". The search strings used in searching the clinical trial databases (clinicaltrials.gov and the ICTRP) were relatively complex and likely to have consequently missed some records (the low number of records retrieved in ICTRP was notable). It is recommended that simple search strings are used to search trial registries.[17] In response to clarification (A1), the company confirmed there was one search run from database inception to 10 May 2024, as described in Appendix D.
Inclusion criteria	B.2.1, Appendix D	In response to clarification (A2), the company confirmed that the clinical SLR covered the full breadth of the proposed marketing authorisation in the decision problem.
Screening	Appendix D	Screening generally followed a standard process with two independent reviewers. Discrepancies were resolved by consensus or the involvement of a third reviewer. However, the EAG noted that there was an initial pre-screening that only involved one reviewer.
Data extraction	Appendix D	Data extraction was quality checked against the original source by a second reviewer rather than independent data extraction by two reviewers. Discrepancies were resolved by consensus.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Tool for quality assessment of included study or studies	Appendix D	Risk of bias for RCTs was assessed using the Centre for Reviews and Dissemination (CRD) risk of bias question set.[18] Risk of bias for non-RCTs and single-arm trials was assessed using ROBINS-1.[19] Risk of bias was assessed by a single reviewer and validated by a second reviewer. The EAG considered the choice of tools to be appropriate.
Evidence synthesis	3.4	The indirect treatment comparison(s) feature a fractional polynomial network meta-analysis, alongside an anchored and unanchored MAIC, and a constant hazard network meta-analysis. The EAG conclude that the fractional polynomial network meta-analysis is the only appropriate analysis presented, although recognise the robustness of the methods used in the alternative scenario analyses.

Abbreviations: CRC, colorectal cancer; CRD, Centre for Reviews and Dissemination; CS, Company submission; dMMR, deficient DNA mismatch repair; EAG, External Assessment Group; ICTRP, International Clinical Trials Registry Platform; MAIC, matching-adjusted indirect comparison; MSI-H, microsatellite instability high; RCT, randomised controlled trial

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

Four studies, described in 18 publications, met the SLR inclusion criteria (Table 6). These comprised one Phase 3 RCT of NIVO + IPI compared to investigator's choice of chemotherapy, one Phase 2 non-randomised trial of NIVO + IPI, one Phase 3 RCT of PEMBRO compared to investigator's choice of chemotherapy, and one Phase 3 RCT of FOLFOX or FOLFIRI ± cetuximab.

Table 6: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
CheckMate 8HW (CM8HW; NCT04008030)	RCT	Untreated dMMR/MSI-H mCRC (n=303).	NIVO + IPI	Investigator's choice of chemotherapy (FOLFIRI or mFOLFOX ± bevacizumab or cetuximab)	Phase 3. Australia, Belgium, Canada, France, Ireland, Italy, Spain, USA.
CheckMate 142 (CM142; NCT02060188)	Non-randomised multi-cohort trial	**Cohort 3:** untreated MSI-H mCRC (n=45).*	NIVO + IPI	None	Phase 2. Australia, Belgium, Canada, France, Ireland, Italy, Spain, USA.
KEYNOTE-177 (KN-177; NCT02563002)	RCT	Untreated dMMR/MSI-H mCRC (n=307).	PEMBRO	Investigator's choice of chemotherapy (FOLFIRI or mFOLFOX ± bevacizumab or cetuximab)	Phase 3. Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Norway, Singapore, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, USA.
CALGB/SWOG 80405 [Alliance] (NCT00265850)	RCT	Untreated, locally advanced or metastatic MSI-H CRC (n=15).	FOLFOX or FOLFIRI with cetuximab	FOLFOX or FOLFIRI without cetuximab	Phase 3. Canada, USA.

Abbreviations: CRC, colorectal cancer; dMMR, DNA mismatch repair deficient; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloridel; IPI, ipilimumab; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability high; NIVO, nivolumab; PEMBRO, pembrolizumab; RCT, randomised controlled trial.

Note: * the CS only presents clinical characteristics and results for Cohort 3.

The company identified CM8HW as the sole trial to provide clinical effectiveness evidence for NIVO + IPI in previously untreated dMMR/MSI-H mCRC, with reference to a relevant comparator. This trial is ongoing and therefore only interim results were available. CM142 was identified as a source of long-term (64 month) follow-up data. This study comprised six Cohorts (depicted in CS Figure 11). Cohort 3 was the first-line MSI-H population. The company only presented characteristics and results from Cohort 3 in the CS as this Cohort was aligned to the target population of the appraisal. Cohort 3 of CM142 was used as supportive evidence because the survival data from CM8HW were comparably less mature (32 months). The EAG considered this to be appropriate. However, the EAG also noted that Cohorts 1 and 2 informed the economic model, and were not profiled in the clinical section of the CS.

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The write up in this section focuses on the two NIVO + IPI trials: CM8HW and CM142. Meanwhile, the comparator trials KN-177 and CALGB/SWOG 80405 used in the NMA are discussed further in Section 3.4.

CMH8HW is an ongoing multi-centre active-controlled Phase 3 RCT, assessing efficacy and safety. There were 3 arms: i) NIVO 240mg + IPI 1mg/kg every 3 weeks for 4 doses, followed by NIVO 480mg every 4 weeks, for a maximum of 2 years; ii) NIVO 240mg every 2 weeks for 6 doses, followed by NIVO 480mg every 4 weeks, for a maximum of 2 years; iii) Investigator's choice of chemotherapy (). fluoropyrimidine regimen [mFOLFOX or FOLFIRI] with or without bevacizumab or cetuximab In response to clarification question A15, the company said that it had not yet been provided these data by its vendor as the prespecified number of events had not been reached.

Participants were randomised in a 2:2:1 ratio. Randomisation to the chemotherapy arm was restricted to patients who had received no more than one prior line of systemic therapy. Randomisation was stratified by number of lines of prior treatment (only results for first line were presented) and primary tumour location (left vs right). There were 88 investigational sites across 22 countries. Of 303 participants randomised, 204 were from the USA, Canada or Europe. 65.6% of participants were from Europe. This is likely to offer fairly good generalisability to a UK clinical practice context. However, the EAG noted that there were only 2 UK participants in the trial, and neither was randomised to treatment arms. The interim analysis datacut presented in the CS for CMH8HW was 12 October 2023.

CM142 is a Phase 2 non-randomised multi-cohort trial of NIVO + IPI. There was no comparator intervention and the different cohorts related to different sub-populations. Cohort 3 addressed the relevant population for this appraisal. The aim of this study was to evaluate 2-year long-term efficacy and safety of NIVO + IPI for first-line dMMR/MSI-H mCRC. In this appraisal, CM142 was used by the company to offer longer-term survival data. NIVO + IPI was dosed as follows: NIVO 3mg/kg + IPI 1mg/kg administered together on day 1 of cycle 1 and then once every 2 weeks (NIVO) or once every 6 weeks (IPI). There were 18 investigational sites across 6 countries: Australia, Belgium, Ireland, Italy, Spain, USA.

3.2.2.2. Population

Trial eligibility criteria

The trial eligibility criteria for CM8HW and CM142 are shown below in Table 7.

Table 7: Key eligibility criteria for pivotal trials

CM8HW	CM142 (Cohort 3)
Aged ≥ 18 years	Aged ≥ 18 years
Histologically confirmed recurrent or metastatic CRC with no prior treatment history with chemotherapy and/or targeted agents for metastatic disease and not amenable to surgery. Participants treated with adjuvant chemotherapy are eligible if disease progression occurred later than 6 months (≥ 6 months) after completion of chemotherapy.	Histologically confirmed recurrent or metastatic CRC with no prior treatment for metastatic disease
Tumour dMMR/MSI-H status confirmed per local practice	Tumour MSI-H status confirmed by accredited laboratory per local practice
Measurable disease by CT/MRI per RECIST v1.1	Measurable disease by CT/MRI per RECIST v1.1
Participants with lesion in a previously irradiation field as the sole site of measurable disease are permitted to enrol provided the lesion(s) have demonstrated clear progression and can be measured accurately	Participants with lesion in a previously irradiation field as the sole site of measurable disease are permitted to enrol provided the lesion(s) have demonstrated clear progression and can be measured accurately
Adequate tumour tissue available. Tumour tissue specimens must be submitted to the central laboratory. Sample must be the same one used for dMMR/MSI-H testing	Willing to provide tumour tissue (archival or fresh biopsy sample)
ECOG PS 0 or 1	ECOG PS 0 or 1
Laboratory test findings: WBC ≥ 2000/uL; neutrophils ≥ 1500/uL; platelets ≥ 100 x 103/uL;	Laboratory test findings: WBC ≥ 2000/uL; neutrophils ≥ 1500/uL; platelets ≥ 100 x 103/uL;

CM8HW	CM142 (Cohort 3)
haemoglobin ≥ 9.0 g/dL; PT/INR and PTT ≤ 1.5 x ULN unless receiving anticoagulant therapy and INR is stable and within recommended range; serum creatinine ≤ 1.5 x ULN unless CLCr > 40 mL/min; AST/ALT ≤ 3.0 x ULN, unless participant has documented liver metastases; bilirubin ≤ 1.5 x ULN, except participants with Gilbert syndrome	haemoglobin > 9.0 g/dL; serum creatinine ≤ 1.5 x ULN unless CLCr ≥ 40 mL/min; AST/ALT ≤ 3.0 x ULN; bilirubin ≤ 1.5 x ULN, except participants with Gilbert syndrome
Women of childbearing potential must have negative pregnancy test, must not be breastfeeding and must agree to follow contraceptive advice (the latter also applies to males unless azoospermic)	Women of childbearing potential must have negative pregnancy test, must not be breastfeeding and must agree to follow contraceptive advice (the latter also applies to males unless azoospermic)

Abbreviations: CT, computed tomography; dMMR, deficient DNA mismatch repair; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; MSI-H, microsatellite instability high; RECIST, Response Evaluation Criteria in Solid Tumours.

Note: Crossover criteria for CM8HW and re-initiation criteria for CM142 are detailed in CS Document B Tables 10 and 20

The EAG considered that the inclusion criteria were generally well-aligned to the final scope for this appraisal, particularly now that the intended MA has been revised to exclude adolescents.

Baseline characteristics

Baseline characteristics for the key included studies are shown below in Table 8. Generally, these trials were fairly similar in baseline profiles. The geographical profile was more US/European in CM142 Cohort 3 than CM8HW, which may be a concern (see Subgroup analysis section). CM142 and CM8HW did not include participants with ECOG 2. The proportion of participants with Lynch syndrome was moderately higher in CM142.

Table 8: Baseline characteristics for trials CM8HW and CM142 (Cohort 3).

	CM8HW			CM142 (Cohort 3)
	NIVO+ IPI (n = 202)	Chemotherapy (n = 101)	Total (n = 303)	CM142 NIVO + IPI (Treated; N = 45)
Age, years, median (min, max)	62.0 (21, 86)	65.0 (26, 87)	[redacted]	66.0 (21, 85)
Sex, n (%)				
Male	95 (47.0)	45 (44.6)	140 (46.2)	23 (51.1)
Region, n (%)				
US/Canada/Europe	133 (65.8)	71 (70.3)	204 (67.3)	Europe [redacted] US [redacted]
Asia	19 (9.4)	11 (10.9)	30 (9.9)	-

	CM8HW			CM142 (Cohort 3)
	NIVO+ IPI (n = 202)	Chemotherapy (n = 101)	Total (n = 303)	CM142 NIVO + IPI (Treated; N = 45)
Other	50 (24.8)	19 (18.8)	69 (22.8)	Australia [redacted]
ECOG PS, n (%)				
0	111 (55.0)	52 (51.5)	163 (53.8)	25 (55.6)
1	91 (45.0)	49 (48.5)	[redacted]	20 (44.4)
Weight, kg, median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Stage at diagnosis, n (%)				
Stage I	[redacted]	[redacted]	[redacted]	
Stage II	43 (21.3)	17 (16.8)	[redacted]	[redacted]
Stage III	73 (36.1)	35 (34.7)	[redacted]	[redacted]
Stage IV	85 (42.1)	49 (48.5)	134 (44.2)	17 (37.8)
Not reported	[redacted]	[redacted]	[redacted]	–
Histological grade, n (%)				
GX	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Cell type, n (%)				
Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Tumour location, n (%)				
Cecum	[redacted]	[redacted]	[redacted]	8 (17.8)
Colon ascending/ hepatic flexure	[redacted]	[redacted]	[redacted]	-
Colon transverse	[redacted]	[redacted]	[redacted]	3 (6.7)
Colon descending/ splenic flexure	[redacted]	[redacted]	[redacted]	-
Colon sigmoid	[redacted]	[redacted]	[redacted]	8 (17.8)
Rectum/ rectosigmoid junction	[redacted]	[redacted]	[redacted]	3 (6.7)
Unknown	[redacted]	[redacted]	[redacted]	Colon NOS 1 (2.2)
Tumour sidedness, n (%)				
Left	64 (31.7)	33 (32.7)	[redacted]	-

	CM8HW			CM142 (Cohort 3)
	NIVO+ IPI (n = 202)	Chemotherapy (n = 101)	Total (n = 303)	CM142 NIVO + IPI (Treated; N = 45)
Right	138 (68.3)	68 (67.3)	206 (68.0)	-
PD-L1 status, n (%)				
≥1%	43 (21.3)	12 (11.9)	55 (18.2)	-
<1%	145 (71.8)	80 (79.2)	225 (74.3)	-
Not evaluable/ indeterminate	[redacted]	[redacted]	[redacted]	-
Not available	[redacted]	[redacted]	[redacted]	-
MSI-H and/or dMMR per central assessment, n (%)				
MSI-H and/or dMMR	171 (84.7)	84 (83.2)	255 (84.2)	[redacted]
MSS and pMMR	21 (10.4)	12 (11.9)	[redacted]	[redacted]
Other	10 (5.0)	5 (5.0)	[redacted]	[redacted]
Lynch syndrome, n (%)				
Yes	22 (10.9)	17 (16.8)	39 (12.9)	[redacted]
No	135 (66.8)	49 (48.5)	184 (60.7)	[redacted]
Unknown	44 (21.8)	30 (29.7)	74 (24.4)	[redacted]
Not reported	1 (0.5)	5 (5.0)	[redacted]	[redacted]

Abbreviations: dMMR, Deficient DNA mismatch repair; ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab; MSI-H, microsatellite instability high; MSS, microsatellite stable; NOS, not otherwise specified; PD-L1, programmed death ligand 1; pMMR, mismatch repair proficient; NIVO, nivolumab; PS, performance status.

Clinical advice to the EAG was that the baseline characteristics in the included trials were generally appropriate to a UK clinical practice context. Around 10% of included participants in CM8HW were of Asian region and ethnicity, while the proportion was lower in CM142. This alleviates a common potential generalisability concern in cancer trials. However, participant weight (median [redacted] for all participants in CM8HW) was considered by clinical advice to the EAG to be an underestimate of patient weight in UK practice, as the UK CRC patient weight is likely to approximate the general population. This has costing implications given dosing of ipilimumab is per kg (see Section 4.2.8.1). The EAG was advised that weight of colorectal cancer patients would be expected to approximate the UK general population.

3.2.2.3. Intervention

The intervention in CM8HW was NIVO 240mg + IPI 1mg/kg every 3 weeks for 4 doses, followed by NIVO 480mg every 4 weeks, for a maximum of 2 years. The intervention in CM142 Cohort 3

was NIVO 3mg/kg + IPI 1mg/kg administered together on day 1 of cycle 1 and then once every 2 weeks (NIVO) or once every 6 weeks (IPI). In response to clarification (A8), the company confirmed that the dose in cohort 3 of CM142 was different than in the other NIVO + IPI cohort and in CM8HW. The intended SmPC (CS Appendix C) states that the recommended dose for first-line treatment of dMMR or MSI-H colorectal cancer is The intended SmPC (CS Appendix C) states that the recommended dose for first-line treatment of dMMR or MSI-H colorectal cancer is 240 mg of nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for a maximum of 4 doses, followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab. The dosing regimen in CM8HW is broadly aligned with the proposed dosing regimen in the SmPC. Within CM8HW patients received a maximum of 2 years of treatment; this is not included in the posology section of the draft SmPC which the EAG note is inconsistent with other indications such as oesophageal squamous cell carcinoma and malignant pleural mesothelioma. The EAG therefore note the importance of specifying the 2 year maximum duration of treatment in the Blueteq form.

The dose of ipilimumab used in CM142 Cohort 3 was not aligned with the CM8HW trial and the proposed dosing regimen in the SmPC (IPI is given 6 weekly rather than 3 weekly. Clinical advice to the EAG and evidence provided in CQ A8 comparing dose schedules in RCC indicated that this should not be expected to have a major impact on outcomes.

The EAG also noted that treatment re-initiation was permitted in CM142, which would not be permitted in practice. This could be an issue in interpreting the available OS data from CM142. No results for the re-initiation cohort specifically were presented in the CS, nor information on its sample size or characteristics. The extent of re-initiation could be important to determining the robustness of CM142 data in the context of this appraisal. The EAG searched the CSR and did not identify any information on how many participants re-initiated, only the criteria by which re-initiation was permitted.

3.2.2.4. Comparator

There were two further arms in CM8HW: NIVO monotherapy 240mg every 2 weeks for 6 doses, followed by NIVO 480mg every 4 weeks, for a maximum of 2 years, and investigator's choice of chemotherapy (mFOLFOX or FOLFIRI ± bevacizumab or cetuximab). The chemotherapy arm in CM8HW did not align well with comparator technologies specified on the NICE final scope,

because bevacizumab is not available in the UK and accounts for a high proportion of participants in the CM8HW comparator arm. The same issue occurred in the pivotal KN-177 trial of PEMBRO in this indication. There was no comparison with PEMBRO which the EAG considered to likely be the key comparator in this appraisal. There was no comparator in CM142.

3.2.2.5. Outcomes

The outcomes reported in the two NIVO + IPI trials are summarised in Table 9.

Table 9: Outcomes reported in the included trials of the technology

	Checkmate 8HW	Checkmate 142
OS	x	✓
PFS*	✓	✓
PFS-2	✓	x
HRQoL	✓	✓
Adverse events	✓	✓
ORR	x	✓
TTNT	✓	✓

Abbreviations: HRQoL, health-related quality of life; PFS, progression free survival; OS, overall survival; ORR, overall response rate, TTNT, time to next treatment.

Note: * per blinded independent central review (BICR) or per investigator.

Due to the objective nature of the survival outcomes, there are no relevant minimally clinically important differences (MCID). The MCID[20] for EQ-5D-3L was +0.08.

Overall Survival

<u>CM8HW</u>

OS is defined as the time from date of randomisation to the date of death due to any cause in CM8HW. Patients who did not die were censored on their last known date alive. In the economic analysis the model structure used implies a surrogate relationship between OS and PFS (in particular that gains in PFS are translated directly to gains in OS as the company base case assumes equal post-progression survival (PPS) across treatments). The appropriateness of a surrogate relationship between PFS and OS was explored by the company based on the post-hoc correlation between PFS and OS from cohort 3 (1L NIVO + IPI) in the CM142 trial

(n=45, median follow-up 52.6 months). The post-hoc analysis used the copula method, which was subsequently evaluated based on statistical goodness-of-fit criteria, visual fit to KM curves, and clinical plausibility of survival extrapolations beyond the follow-up period. Correlation strength was measured by Spearman's rho, these methods are discussed below. Overall, conclusions regarding OS had very limited interpretability, and the EAG were limited in the appraisal of surrogacy between PFS and OS.

CM142

OS by investigator or BICR (not clearly stated in CS if it was one either/or endpoint or two separate endpoints) was a key exploratory endpoint. OS was defined as the time from first dosing date to the date of death. Patients who did not die were censored at their last known date alive. As OS is an objective endpoint, external assessment is not required.

As above, the appropriateness of the surrogate relationship between PFS and OS in CM8HW, relied upon the correlation strength measured using spearman's rho, determined via the copula method, based on PFS and OS data from CM142 cohort 3 (n =45). The copula method provided different fits for the dependence between PFS and OS in this scenario, allowing for flexible modelling of the data. Five copula functions (Clayton, Frank, Hougaard, Joe, and Plackett) were used to model the joint PFS-OS distribution. These copula functions encompassed a representative variety of archetypal behaviours for the dependence of two distributions. This method was combined with commonly used parametric distributions to model the PFS and OS curves. Joint PFS-OS models were evaluated based on statistical goodness-of-fit criteria, visual fit to KM curves, and clinical plausibility of survival extrapolations beyond the follow-up period.

Estimates of rho and its 95% CI were similar across a range of copula functions (rho 0.82-0.95); the company presented the preferred copula model correlation (Frank: 0.92 [95% CI: 0.78-0.98]) suggesting a strong positive correlation. It was encouraging that the range of estimates for Spearman's Rho were similar, suggesting that all estimates indicated a strong positive correlation, giving confidence in the estimate, and fit of the data across copula functions. However, this analysis did not inform whether the assumption in the model that incremental gains in PFS between arms translated to incremental gains in OS was reasonable or not. Furthermore, the EAG noted the immaturity of a sample size of 45 in CM142, of which MSI-H status was only centrally confirmed in 10 of these cases; the remaining 33 cases were not assessed.

Furthermore, regarding the parametric distributions of PFS and OS curves, generalized gamma and Gompertz distributions were selected to model the PFS and OS curves, respectively. The EAG had concerns regarding the preferred parametric distributions chosen for the OS curve. The Gompertz distribution was suited for exponentially increasing or decreasing hazard rates, which the EAG believe was optimistic for these data.

Overall, the EAG concluded that the general statistical theory was sound, yet it was difficult to appraise the implications of the surrogacy of this method without parallel analysis or validation versus observed OS for the CM8HW trial, which was not provided, as well as the limitations in sample size and generalisability described above. Similarly, the EAG asked for RMST differences and hazard ratio estimates to further quantify the practical impact of the surrogacy, but these were not provided. As a result, the EAG concluded that the surrogacy analysis has limited usefulness.

Progression Free Survival

CM8HW

PFS was defined as the time from date of randomisation to date of first objectively documented disease progression per RECIST 1.1, or death due to any cause, whichever occurred first. PFS was presented for three different definitions; by BICR in all randomised patients, per BICR in the centrally confirmed population, and per investigator in the centrally confirmed population. The company presented the primary outcome PFS by BICR for NIVO + IPI vs. chemotherapy, in the first line population, in those with centrally confirmed dMMR/MSI-H status. The EAG agreed with the use of centrally confirmed dMMR/MSI-H status within the primary outcome as this is the most valid assessment of dMMR/MSI-H status. However, the ITC used all randomised patients, in lieu of a centrally confirmed population within the KN177 trial, and this limited the robustness of this analysis – although it may provide greater generalisability as central confirmation is not undertaken in clinical practice. In the interim analysis (final analysis not yet available), PFS was compared via a two-sided max-combo test when the PH assumption did not hold. The EAG disagreed with the use of a max-combo test as it upweights later events where the treatment effect is more pronounced, for which there was limited evidence. This increased the risk of type 1 error. We considered the HR from the max-combo tests to be less credible. Weighting all events equally in a standard log-rank test is a more conservative strategy despite the challenges with applying a summary standard measure from a Cox proportional hazards model over the entirety of the time horizon.

The company compared secondary outcomes PFS per BICR in all randomised patients, and PFS per investigator in the centrally confirmed population, using the log-rank test. Of note, the main outcome version in the ITC is PFS per BICR in all randomised patients (as above). PFS curves were estimated using the KM product-limit approach. Median PFS with two-sided 95% CIs were computed using the Brookmeyer and Crowley method with log-log transformation. The EAG considered these methods were acceptable and credible.

Tumour assessment was conducted using CT and MRI of the chest, abdomen, pelvis, and all known sites of disease at baseline, every 6 weeks from treatment assignment for the first 24 weeks, and every 8 weeks thereafter, until either progression is confirmed or treatment is discontinued, whichever occurs later (up to week 96), every 16 weeks until progression is confirmed (weeks 97 to 144), and every 24 weeks until progression is confirmed (beyond week 144). PFS censoring rules were as follows:

- Patients who died without a reported prior progression and without initiation of subsequent anti-cancer therapy were considered to have progressed on the date of their death.
- Patients who did not progress or die were censored on the date of their last tumour assessment.
- Patients who did not have any on-study tumour assessments and did not die were censored at the randomisation date.
- Patients who received subsequent anti-cancer therapy or crossed over to receive treatment aligned to another arm of the trial, prior to documented progression, or with no documented progression, were censored at the date of the last evaluable tumour assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy/crossover.

An alternative definition of PFS per BICR, which did not include censoring for subsequent treatment (also known as the EMA definition), was presented for all randomised patients and in the centrally confirmed population. In CM8HW, PFS2 per investigator in the centrally confirmed population was another exploratory endpoint. PFS2 was defined as the time between randomisation and the second disease progression, or death from any cause, used to assess the effect of treatment after disease progression.

CM142

PFS was defined as the time from first dosing date to the date of first documented progression, as determined by investigator/BICR (it was not clearly stated in the CS if it was one either/or endpoint or two separate endpoints), or death from any cause, whichever occurred first. For cohort 3, PFS was summarised descriptively using the KM product-limit method. Median values, along with two-sided 95% CIs based on log-log transformation, were also calculated. KM curves for PFS were generated. PFS rates at specific timepoints were estimated using KM estimates and associated two-sided 95% CIs were calculated. The EAG considered these methods were acceptable and interpretable. OS will be assessed using the same approach when available.

Tumour assessment was conducted using CT and/or MRI scans of the chest, abdomen, pelvis, and all known sites of disease at baseline, 6 weeks from first dose, every 6 weeks until week 24, and then every 12 weeks after week 24.

The company presented three censoring rules for PFS:

- Patients who did not progress or died were censored on the date of their last evaluable tumour assessment.
- Patients who did not have baseline on-study tumour assessments and did not die were censored on the first dosing date.
- Patients who initiated any subsequent anti-cancer therapy without prior recorded progression were censored at last evaluable tumour assessment prior to initiation of subsequent therapy

Analysis was not presented in the CS using the EMA definition for subsequent treatment, but was provided in response to clarification questions.

Overall Response Rate

CM8HW

Overall Response Rate (ORR) was a key secondary endpoint, assessed in those with confirmed dMMR/MSI-H. ORR was defined as the proportion of all randomised participants whose best overall response (BOR) – between date of first study drug and date of initial progressed disease per RECIST v1.1, or date of subsequent therapy, whichever occurred first – was either confirmed complete response (CR) or confirmed partial response (PR).

CM142

The primary outcome in CM142 was tumour response, as described by ORR, duration of response, and complete response rate, assessed per investigator. The same tumour response measures, assessed by BICR, were secondary endpoints. ORR was defined as the number of participants with a BOR – between date of first study drug and date of initial progressed disease per RECIST v1.1, or date of subsequent therapy, whichever occurred first – of CR or PR, divided by the number of treated participants.

Time to next treatment

TTNT is available for both CM8HW and CM142. It was provided in response to an EAG clarification question, but was not a pre-specified endpoint, meaning details of how it was assessed were not available.

Adverse Events

CM8HW

The exploratory safety endpoints were incidence of adverse events and serious adverse events, adverse events leading to discontinuation (with or without relationship to the study drug), and deaths. Selected adverse events and immune-mediated adverse events were recorded separately. Adverse events were recorded and graded according to CTCAE. Adverse events of special interest were selected based on the following rules:

- AEs that may differ in type, frequency, or severity from AEs caused by non-Ios.
- AEs that may require immunosuppression as part of their management.
- AEs whose early recognition and management may mitigate severe toxicity.
- AEs for which multiple event terms may be used to describe a single type of AE.

AEs were recorded at each visit; information was collected for a minimum of 100 days following discontinuation of study treatment.

CM142

The exploratory safety endpoints were rate of deaths, adverse events, serious adverse events, and adverse events leading to discontinuation. Incidence of safety outcomes was assessed. Events of special interest were graded using NCI CTCAE version 4.0. Adverse events were

assessed by investigators and assessed as on-treatment if the event occurred within 30 days of the last dose of study treatment, or 100 days for analyses specified as extended-follow-up.

3.2.2.6. Critical appraisal of the design of the studies

The company presented critical appraisal of the pivotal CM8HW and CM142 trials in CS Tables 15 and 25. The EAG broadly agreed with the company's assessment. The EAG considered that a blinded trial would have offered lower risk of bias.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

Results are presented for outcomes in the order listed on the NICE scope. Data on adverse events are presented in a separate section below, as customary.

The EAG noted that in CM8HW, [redacted] participants crossed over from chemotherapy to NIVO + IPI as a result of disease progression. However, as NIVO + IPI is available as a subsequent treatment in practice, this crossover does not represent a deviation from available UK treatments. The EAG also noted that while CM8HW had three arms, no results for the NIVO monotherapy arm were provided, either in the CS or in response to the EAG's clarification questions. The company justified this (clarification response A15) by saying that pre-specified statistical testing hierarchy event numbers had not been reached in this arm and that "releasing the NIVO monotherapy results prematurely could compromise the trial's integrity, potentially introducing bias and variability that may lead to misleading interpretations". The company indicated that the earliest it will provide NIVO monotherapy results would be late Q4 2024 (clarification question A15).

Analysis populations in the two pivotal trials are profiled below in Table 10.

Table 10: Analysis populations in the two pivotal trials

	CM8HW	CM142
Enrolled	All patients who signed an informed consent form and were registered into the IRT system	NA
Randomised	All patients randomised to any arm	NA

	CM8HW	**CM142**
Confirmed dMMR/MSI-H	All randomised patients who have centrally confirmed dMMR/MSI-H status by central test per IHC or PCR	NA
MSI-H	NA	Patients defined as MSI-H based on standard diagnostic testing, including those confirmed in the current study using PCR
Treated	All patients who received at least one dose of study treatment	All patients who received at least one dose of study medication
Response evaluable	All randomised patients who have baseline and at least one on-study evaluable tumour measurement. This population was defined based on Investigator and BICR data.	All patients who have evaluable tumour measurement at baseline, plus at least one on-study evaluable measurement
Outcomes research	All randomised patients who have an assessment at baseline and at least one subsequent post-baseline assessment (for EORTC QLQ-C30, QLQ-CR29 and EQ-5D-3L separately)	All treated patients who have an assessment at baseline, plus at least one subsequent assessment, for either of the EORTC QLQ-C30 or EQ-5D questionnaires
Crossover cohort	All randomised patients who received at least one dose of study treatment following crossover to the NIVO + IPI arm	NA
Re-initiation	NA	All patients who received at least one dose of study drugs following treatment re-initiation

Abbreviations: dMMR, deficient DNA mismatch repair; EQ-5D, EuroQoL 5 Dimensions; EORTC QLQ, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IPI, ipilimumab; MSI-H, microsatellite instability high; NA, not applicable; NIVO, nivolumab; PCR, Polymerase chain reaction.

The primary analysis population for the primary endpoint comprised those whose dMMR/MSI-H status has been centrally confirmed.

Overall survival

CM8HW

OS data from CM8HW were not presented in the CS. OS is the endpoint listed first on the NICE scope, arguably the most important endpoint in oncology[21] and a key driver of the economic

model. The company said that it had not yet been supplied OS data form the pivotal trial by its vendor as the prespecified number of events had not yet been reached. (clarification response A21). In the clarification question, the EAG stated that it was aware that the data would not be mature and would be treated as such, but that provision of these data was essential to enable appropriate model validation. The EAG noted that at the time of the interim analysis (12 October 2023), the information fraction was 80%, suggesting that OS data at this point in time would likely closely parallel the final OS data. The company justified its position based on the hierarchical statistical testing strategy pre-specified in the trial protocol and to "preserve the trial's integrity and to avoid introducing bias that could potentially lead to inaccurate conclusions". The EAG considered that the production of an ad hoc confidential analysis for regulatory and decision-making purposes would be standard and that the company's decision not to do this is a major issue for the appraisal. The EAG note that of the 5 appraisals listed in the CS as being ones where OS data was not provided:

- OS data was provided in TA709: a competitor submission in the same indication with a similar level of data maturity at the time of submission
- OS data was provided in TA716
- OS data was provided in TA400 after the initial submission prior to the Committee meeting (see page 879 of the Committee papers for example)

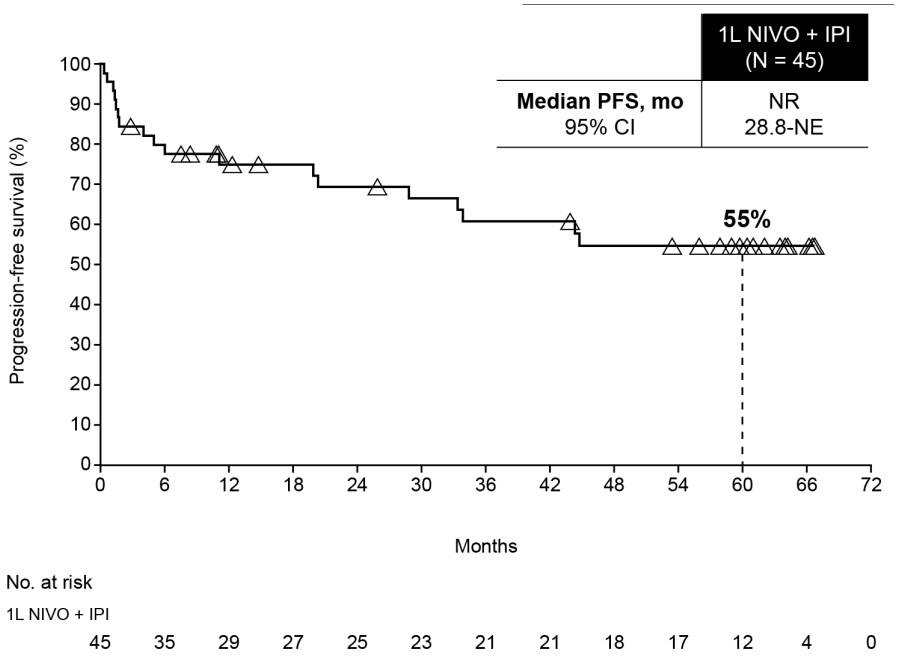
The other two submissions (TA817 and TA746) are in the adjuvant space where their OS is expected to be less mature and disease-free survival likely to be more predictive of OS due to the potential for cure following surgery.

The EAG also noted that deaths are a safety endpoint in this trial and therefore the company has access to death data.

<u>CM142</u>

Median OS was not reached at 64.2 months follow-up. At 60 months, the OS rate was 67%. Patient-level correlations between OS and PFS ranged from r=0.82 to r=0.95 (Spearman's rho correlation). The KM for PFS is shown in Figure 3.

Figure 3: KM curve for PFS for CM142



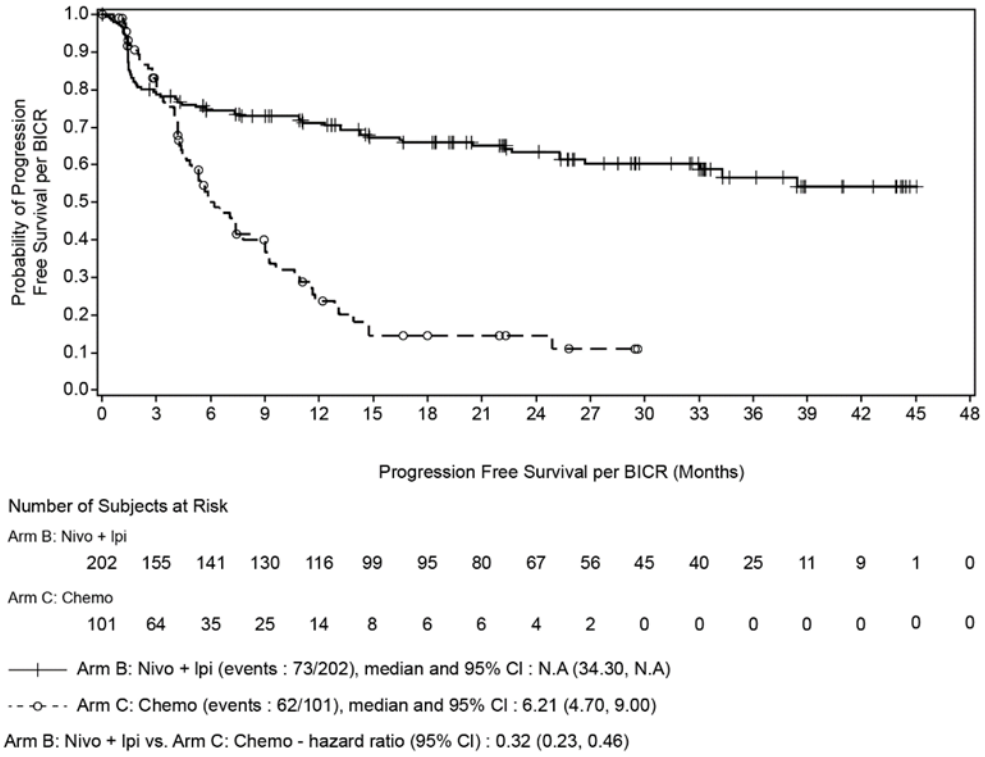
Abbreviations: IPI, ipilimumab; KM, Kaplan Meier; mo, months; NIVO, nivolumab; NR, not reached; PFS, progression-free survival

Progression-free survival

CM8HW

Assessed by BICR, NIVO + IPI showed a statistically significant benefit for NIVO + IPI compared to chemotherapy, in all randomised patients (HR 0.32, 95% CI 0.23, 0.46). In the NIVO + IPI arm, median PFS was not reached after [redacted] months of follow-up. In the chemotherapy arm, median PFS was [redacted] months. KM curves show separation three months post-randomisation (Figure 4). Curves crossed initially, which the EAG did not consider to be unexpected. The company referred to this improvement as 'clinically meaningful', although did not establish a MCID. The EAG considered that the use of MCIDs would not be expected for mortality-related outcomes, which are objective in nature.

Figure 4: CM8HW KM curves for PFS per BICR in all randomised participants

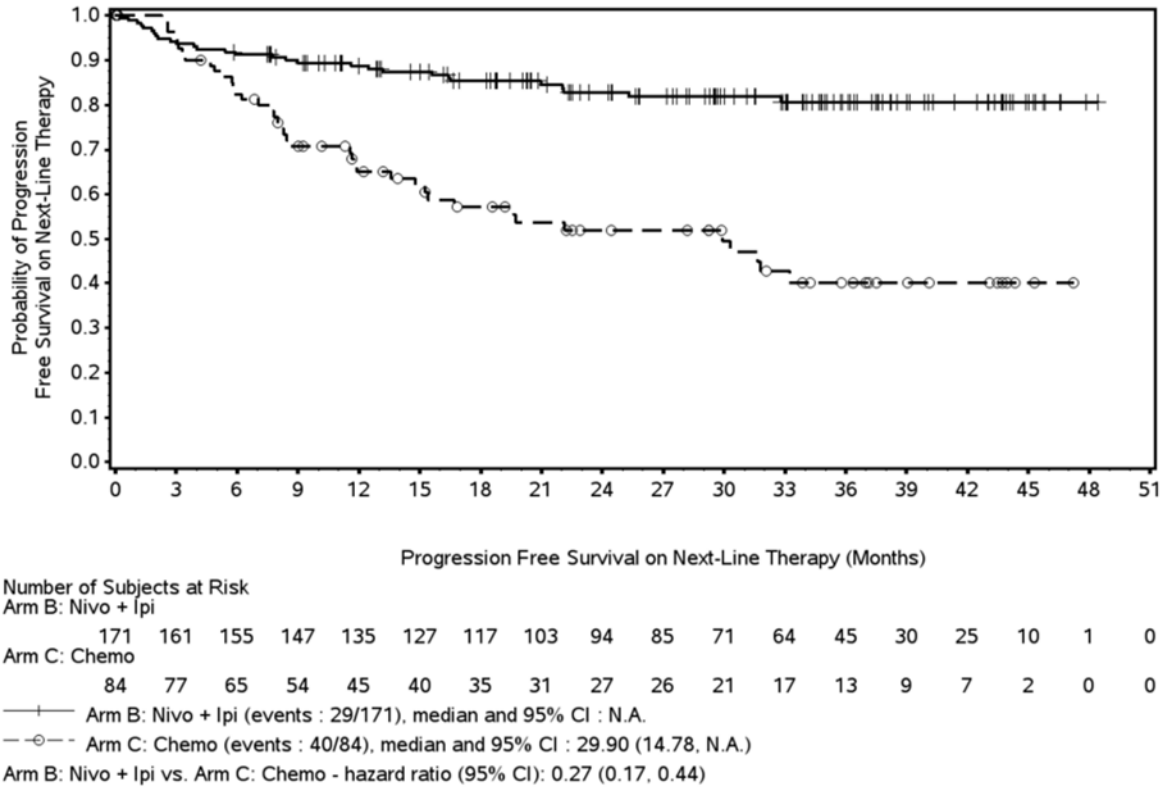


Abbreviations: BICR, blinded independent committee review; CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; NA, not available; PFS, progression-free survival

In the centrally confirmed population, NIVO + IPI showed a statistically significantly greater improvement in PFS per BICR compared to chemotherapy (HR via Cox test [redacted] HR via max-combo test [redacted] This was considered clinically meaningful in the CS. Median PFS was not reached after 31.6 months of follow-up in the NIVO + IPI arm. After a comparable period of follow-up, the chemotherapy arm had a median PFS of 5.9 (4.4, 7.9) months. Results were similar for PFS per investigator.

Alternative PFS estimates using the EMA definition, which avoids the risk of informative censoring, were provided in response to the clarification questions (A29). Censoring would be expected to benefit the chemotherapy arm. A statistically significant benefit for NIVO + IPI compared to chemotherapy remained (HR 0.33 (95% CI: 0.23, 0.45), compared with 0.32 (95% CI: 0.23, 0.46) for the primary definition. PFS-2 for both available arms in CM8HW is shown in Figure 5, demonstrating an advantage for NIVO + IPI over chemotherapy.

Figure 5. Progression-Free Survival on Next Line of Therapy (PFS2) for NIVO + IPI vs Chemo - All 1L Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC



Abbreviations: 1L first line; CI, confidence interval; dMMR, deficient DNA mismatch repair; IPI, ipilimumab; MSI-H, microsatellite instability high; NIVO, nivolumab; NA, not available; PFS, progression-free survival

CM142

Median PFS was not reached at 64.2 months follow-up. At 60 months, the PFS rate was 55%. This appears to match fairly well to the PFS data in CM8HW as shown in Figure 4.

Response rates

CM8HW

Response rate data were not provided for CM8HW in the CS. The company stated that it would only provide data from secondary outcomes once the trial was complete, rather than in interim analyses. The EAG was not particularly concerned about the absence of response rate data, as they are not pivotal in driving the economic modelling.

CM142

ORR was 71% (95% CI 56-84%). The BOR was CR in 20% of participants, PR in 51%, SD in 13% and PD in 16%. The DCR was 84%. Mean TTR was 2.7 months (range 1.2 – 27.7). Duration of response was not reached.

Health-related quality of life

CM8HW

There was no statistically significant difference in baseline mean EQ-5D-3L scores for the NIVO + IPI and chemotherapy arms ([redacted] for both). There was a trend towards improvement in the NIVO + IPI arm and worsening in the chemotherapy arm over time. The improvement in the NIVO + IPI arm met the MCID. Results are presented in the CS as mean change from baseline – no mean (SD) follow-up scores are provided.

CM142

No health-related quality of life results for CM142 were presented in the CS. The EAG did not consider this a concern since the EQ-5D-3L results from CM8HW were those that drove the utilities in the economic model and comparative data are not available.

Subgroup analyses

CM8HW

The centrally confirmed population for PFS was stratified by tumour sidedness in a pre-specified subgroup analysis. A series of subgroup analysis results for the primary endpoint were presented, although the company said that the results presented were selected not exhaustive. Post-hoc subgroup analyses were conducted by whether participants received bevacizumab-containing and cetuximab-containing regimens respectively. The rationale for the subgroup on bevacizumab was because this treatment was included in the trial but is not used in UK clinical practice in this indication. The rationale for the cetuximab subgroup was because cetuximab has been considered (TA709) to have comparable efficacy to panitumumab, which is also used in UK clinical practice but was excluded from the trial. Pre-specified subgroup results for the primary PFS endpoint are shown in Table 11. Results for post-hoc analysis of PFS for all randomised participants per BICR by chemotherapy regimen are shown in Table 12. It was noted that the PFS HR for NIVO + IPI vs chemotherapy was [redacted] in

US/Canada/Europe (combined) than other localities. The effect was also [redacted] in those with higher PD-L1 expression. PFS was [redacted] in bevacizumab-containing than cetuximab-containing regimens. Bevacizumab is not used in the UK. This result indicates that the company's comparison to UK chemotherapy is probably conservative as they assume that UK chemotherapy is the same as chemotherapy in CM8HW. It was also noted (clarification response A24) that that were no statistically significant interaction terms for any of the subgroups.

Table 11: CM8HW subgroup analysis for PFS in centrally confirmed population (interim analysis)

		NIVO + IPI		Chemotherapy	
	N	**PFS (95% CI)**	**N**	**PFS (95% CI)**	**HR (95% CI)**
Total	202	NR (38.4-NE),	101	5.9 (4.4-7.8).	0.21 (0.13-0.35)
Age					
< 65	98	NR [redacted]	40	5.68 (4.24, 10.91)	0.19 [redacted]
≥ 65	73	NR [redacted]	44	5.85 (4.01, 7.79)	0.24 [redacted]
≥ 65 and < 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region					
US/Canada/ Europe	109	NR [redacted]	58	5.68 (4.21, 9.26)	0.27 [redacted]
Asia	17	NR	11	7.39 (1.45, NR)	0.03 [redacted]
Rest of world	45	NR [redacted]	15	6.21 (3.35, 9.23)	0.16 [redacted]
ECOG PS					
0	97	NR [redacted]	45	9.00 (5.68, 10.91)	0.22 [redacted]
1	74	NR [redacted]	39	4.21 (2.56, 5.36)	0.20 [redacted]
Liver metastasis					
Yes	55	NR [redacted]	32	5.85 (4.30, 9.23)	0.11 [redacted]
No	114	NR [redacted]	52	5.36 (4.21, 9.59)	0.28 [redacted]
PD-L1 status					

≥ 1%	43	NR	12	3.35 (1.28, 7.10)	0.11
<1%	122	NR	69	6.47 (4.70, 9.26)	0.22
Mutation status					
BRAF/KRAS/NRAS WT	41	34.30	17	5.36 (1.45, 7.39)	0.08
BRAF mutant	50	NR	22	9.23 (4.24, NR)	0.37
KRAS or NRAS mutant	30	NR	15	5.68 (1.41, 14.75)	0.24

Abbreviations: CI, confidence interval; CM, CheckMate; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; NR, not reached; PD-L1, programmed death ligand 1; PFS, progression-free survival; PS, performance status

Table 12: CM8HW PFS results for all randomised subjects per BICR (interim chemotherapy sub-group analysis)

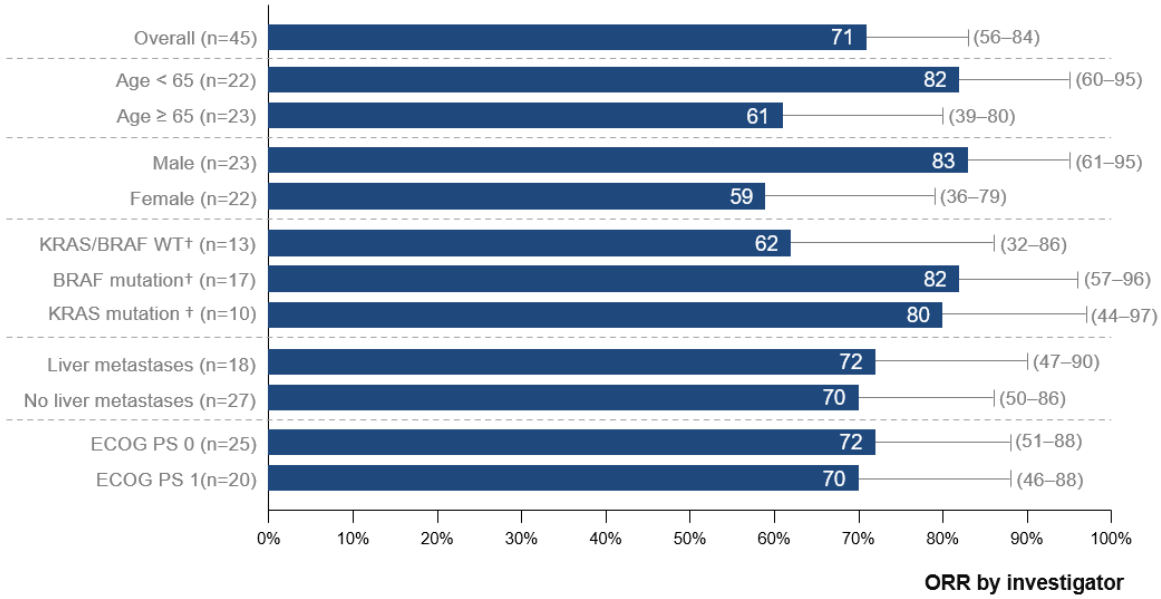
		Bevacizumab containing regimen	**Cetuximab containing regimen**	**No bevacizumab or cetuximab**	**Chemotherapy**
N		56			101
PFS (BICR)	Events, n (%)				
	Median (95% CI), months				
PFS rate, % (95% CI)	6 months				
	12 months				
	24 months				

Abbreviations: BICR, blinded independent central review; CM, CheckMate; CI, confidence interval; PFS, progression free survival

CM142

Pre-specified subgroups for ORR were assessed, as detailed in the figure below. ORR was not shown to be significantly different across subgroups (Figure 6).

Figure 6: Tornado plot for CM142 ORR subgroup analysis



Abbreviations: ORR, Overall response rate

Adverse effects

CM8HW

Treatment duration was longer on NIVO + IPI than chemotherapy (median duration 13.5 vs 4.0 months). Tolerability was nevertheless superior on NIVO + IPI with fewer treatment-related adverse events (TRAEs; 80.0% vs 94.3%), fewer grade 3 or 4 TRAEs (23.0% vs. 47.7%), and fewer TRAEs leading to discontinuation (16.5% vs. 31.8%). In the group randomised to NIVO + IPI, there were 2 deaths due to study drug toxicity, whereas in the group randomised to chemotherapy, there was one. However, this was a crossover patient, and the death was attributed to NIVO + IPI treatment. The most frequent categories of treatment-related adverse events were skin [redacted] endocrine [redacted], gastrointestinal [redacted] and hepatic [redacted]. The only category with grade 3 or 4 treatment-related adverse events occurring in at least 5% of participants was endocrine [redacted]

CM142

There were 9 (20%) grade 3 or 4 serious treatment-related adverse events, 7 (16%) treatment-related adverse events leading to discontinuation, and one treatment-related death. The most common categories of treatment-related adverse events with potential immunologic aetiology were skin (49%), endocrine (29%), gastrointestinal (20%) and hepatic (11%). There were no grade 3 or 4 treatment-related adverse events with potential immunologic aetiology that occurred in ≥5% of participants.

TTNT

TTNT KM plots are provided below for CM8HW NIVO + IPI (Figure 7), CM8HW chemotherapy (Figure 8) and CM142 all 1L (Figure 9).

Figure 7. KM plot of time to next treatment for CM8HW NIVO + IPI all treated

Abbreviations: CI, confidence interval; IPI, ipilimumab; KM, Kaplan Meier; NIVO, nivolumab

Figure 8. KM plot of time to next treatment for CM8HW chemotherapy all treated

Abbreviations: CI, confidence interval; IPI, ipilimumab; KM, Kaplan Meier; NIVO, nivolumab

Figure 9. KM plot of time to next treatment for CM142 NIVO + IPI all 1L

Abbreviations: 1L, first line; CI, confidence interval; IPI, ipilimumab; KM, Kaplan Meier; NIVO, nivolumab

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Two studies from the SLR were used in the primary network, comparing NIVO + IPI with PEMBRO. These were CM8HW (as profiled above) and KN-177. CM142 was not included in the network. The other included study from the SLR, CALGB/SWOG 80405, assessed FOLFOX or FOLFIRI ± cetuximab and as such was not eligible for inclusion in the NMA network. A sensitivity network was also conducted including panitumumab + FOLFOX through the PRIME trial.[22] This had not been identified through the company's SLR as it did not specify a dMMR/MSI-H population (clarification question A5), therefore reflecting a broader mCRC population.

The study characteristics of KN-177 are presented in Table 6. This was an RCT comparing PEMBRO and standard therapy in participants with MSI-H or dMMR Stage IV CRC.[23] All participants had ECOG performance status 0 or 1, had adequate organ function, measurable disease and had life expectancy of at least 3 months. The primary endpoints were PFS per RECIST 1.1 as assessed by central imaging vendor (up to approximately 59 months) and OS (same time frame). ORR per RECIST 1.1 as assessed by central imaging vendor, adverse events and discontinuations due to adverse events were secondary outcomes.

PRIME[24] was a Phase 3 RCT (n=1,183 randomised) of panitumumab with FOLFOX versus FOLFOX for first-line mCRC. All participants had ECOG 0 to 2. Randomisation was stratified by geographic region (Western Europe, Canada and Australia vs rest of the world). The primary endpoint was PFS by blinded central radiology review. The secondary endpoint was OS. Information on time to subsequent treatment, ORR, resection rate, quality of life and safety were also reported.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

The ITC analyses undertaken compare PFS per BICR in all randomised subjects. The EAG noted that there was a lack of clarity regarding the PFS outcome used in the ITC in Doc B, regarding the use of all randomised patients vs those centrally confirmed. The EAG have since confirmed all randomised patients are used. The company presented four ITC options: 1) fractional polynomial network meta-analysis (FPNMA), 2) anchored MAIC, 3) constant hazard network meta-analysis, and 4) unanchored MAIC. The company asserted, and the EAG agreed, that the most appropriate ITC was the fractional polynomial network meta-analysis, and that the

alternative ITCs were presented as validating scenario analyses only. For this reason, the EAG focussed its appraisal on the fractional polynomial network meta-analysis, as this was the most appropriate model for decision making (and providing brief commentary on the alternative anchored MAIC and constant hazard network meta-analysis solution). The EAG have not sought to provide details regarding the unanchored MAIC as this model was inappropriate for decision making in this context given other options available.

3.4.1. FPNMA

3.4.1.1. Definition

The fractional polynomial network meta-analysis is a method of indirect comparison which combines fractional polynomial regression and network meta-analysis principles to pool data from multiple studies using a common comparator. The FPNMA is particularly useful for capturing non-linear relationships between treatment effects and covariates, as well as when the assumption of proportional hazards does not hold, as was the case in CM8HW, estimating a time-varying hazard ratio in this context is most appropriate. Notably, the company presented a thorough assessment of the validity of the proportional hazards assumption, including a visual inspection of the scaled Schoenfeld residuals plot against time, as well as the log-cumulative hazard plot against log-time, for patients receiving NIVO + IPI versus chemotherapy. The EAG agreed with the company's decision to reject the proportional hazards assumption.

3.4.1.2. Feasibility and transitivity

Benefits of a FPNMA include a flexible fit as it allows the baseline hazard function and relative treatment effect (the hazard ratio) to vary over time, making for a 'higher-fidelity' fit to the trial data. In order to select studies for inclusion in any NMA, studies must meet assumptions of transitivity, consistency, and homogeneity. The company justified not presenting formal tests of consistency and heterogeneity due to singular closed loops and single evidence sources, respectively. The EAG agreed with this decision.

In addition, transitivity of the network relies on the generalisability of centrally vs. locally tested microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) status. In the CM8HW trial, dMMR or MSI-H was initially locally confirmed, of which 15% of these cases, when re-tested centrally, were determined not to be dMMR or MSI-H and were excluded from the primary endpoint analysis. On the contrary, in KN-177, dMMR/ MSI-H status was locally confirmed with no follow-up central confirmation. Due to the limitations of local testing in the

KN177 trial, it was appropriate to compare all randomised patients in the ITC. The EAG considered the use of central testing important for preventing non-differential ascertainment bias, when drawing conclusions specific to MSI-H/ dMMR status.

Transitivity of the network also relied on the assumption of a class treatment effect, particularly relevant to the control arms. The company presented evidence that within the chemotherapy arms of CM8HW and KN-177, they were similar enough for comparison. Yet some heterogeneity in outcomes may be explained by the percentage of patients receiving bevacizumab (CM8HW = 64% vs. KN-177 = 70%), which is not used in UK practice. In TA709 it was considered appropriate to consider bevacizumab-containing regimens to have efficacy analogous to cetuximab-containing regimens. However, the EAG noted that this added a level of uncertainty to the estimate and stressed the importance of understanding this class effect in the applicability of the ITC in clinical and policy decision-making.

3.4.1.3. Statistical methods

The company tested multiple power solutions for order 2 in the fractional polynomial model. Of these models, the company presented four criteria for final model selection for the FPNMA primary network. 1) Lowest deviance information criterion (DIC) among the models that did not demonstrate non-convergence (Table 13), 2) Rhat statistic (> 1.01 indicates non-convergence), 3) manual inspection of trace plots and posterior density functions, 4) manual inspection on the predicted vs observed survival function. The use of batch curve selection may have precluded a careful selection based on visual fit and plausibility. Aside from this risk, the EAG agreed with the appropriateness of these criteria.

Table 13: Fixed effects model selection by DIC, PFS, primary network

Selection	Model	DIC	Maximum Rhat	N iterations / samples
Primary analysis	[redacted]	[redacted]	[redacted]	[redacted]
First sensitivity	[redacted]	[redacted]	[redacted]	[redacted]
Second	[redacted]	[redacted]	[redacted]	[redacted]

sensitivity				
First rejection	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DIC, deviance information criterion; PFS, progression-free survival

The batch curve selection process yielded a primary model and two sensitivity models. The power solutions included -0.5 and -0.5 in the primary and first sensitivity model, and -1 and 0 in the second sensitivity and first rejection models. Time-varying relative treatment effects were tested for each power solution (110 and 111): the 110 term indicates that there is a treatment effect on the constant component and on the first power term, but not on the second power term, whereas 111 indicates that there is a treatment effect on each of the power terms.

The EAG concluded that the methods used to assess hazard profiles were robust and well fitted in the primary network and agreed that the primary model had good visual fit to the trial data. The sensitivity models showed an equally good statistical fit.

3.4.1.4. Primary network results

Comparisons between NIVO + IPI and PEMBRO on the basis of time-specific HRs and associated credible intervals (CrI) suggested that NIVO + IPI had a significantly lower rate of PFS events compared to PEMBRO between 6 months ([redacted]), with an increasing relative treatment effect over time. The comparison between NIVO + IPI and chemotherapy in the primary analysis reflected a significantly lower risk of event and a treatment effect, which improves over time [redacted] Notably, in either scenario, the CrIs did not cross the null, suggesting confidence in the finding that the benefits of NIVO + IPI consistently outweigh the comparators.

The shape of the relative hazard functions in Figure 10 diverge over time, indicative of a greater benefit of NIVO + IPI over chemotherapy, than over PEMBRO. Of note, there was a steep reduction in the hazard ratio in the NIVO + IPI vs chemotherapy group between 0 and 6 months, underscoring the rapid onset of benefit. The reduction in hazard function continued up to 84 months. Conversely, the relative hazard function for NIVO + IPI vs PEMBRO suggested a more stable effect over time, with an initial steep reduction in the hazard ratio between months 0 and 6, and then a continued, gradual decrease in hazard up to month 84. The first and second

sensitivity models for PFS per BICR in all randomised patients showed a sensitivity to the FPNMA model fit, with a more flexible model fit demonstrating a less optimistic estimate.

Figure 10: PFS hazard ratios–- NIVO + IPI versus all comparators – Primary network–- Primary model

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival; SoC, standard of care

At clarification, the company presented the primary network comparing KN-177 PFS per BICR in all randomized patients, to CM8HW PFS per investigator in all randomized patients, and PFS per BICR in the centrally confirmed population. The EAG understood that KN-177 did not include a centrally confirmed cohort and that therefore a comparison between centrally confirmed populations was not possible to make. However, the EAG did not understand why the company did not update the data for KN-177 in the PFS per investigator comparison, and this remains a concern. At present, these additional analyses violate the assumption of transitivity across the network, and therefore the EAG did not interpret these analyses. Nevertheless, the company's presentation of first and second sensitivity model for PFS per investigator in all randomized patients suggested that, per investigator, the hazard function is sensitive to the

model fit, and greater flexibility shows less optimistic estimates. The effect of FPNMA model appeared more pronounced in PFS per investigator than in PFS per BICR.

3.4.1.5. Sensitivity network results

The company presented a sensitivity network, including an additional trial, PRIME, for the primary network (all randomised patients). The company noted that vs. PEMBRO, the findings were consistent with the primary network. Inclusion of the additional PRIME trial allowed for the comparison between NIVO + IPI and panitumumab + FOLFOX. The network inferred that there is an increasing and significant hazard ratio between 6 and 60 months in favour of NIVO + IPI.

Similarly, in the sensitivity network comparing NIVO + IPI to chemotherapy, PEMBRO, and PAN + FOLFOX, the time-varying hazard ratios for NIVO + IPI vs. PEMBRO were consistent with the primary network, indicating a robust outcome. The decreasing and significant hazard ratio over 6-60 months for NIVO + IPI vs. PAN + FOLFOX suggested NIVO + IPI have a comparatively greater treatment effect over time and could influence long-term treatment strategies.

The shape of the relative hazard functions in Figure 11 indicated steep reductions in the hazard ratio of NIVO + IPI vs pan + FOLFOX and vs chemotherapy between 0 and 6 months, reflecting the rapid onset in benefit. The reduction in hazard ratio continued up to 84 months in the NIVO + IPI vs PAN + FOLFOX comparison, whereas this became more stable in the NIVO + IPI vs chemotherapy comparison. As seen in the primary analysis, the NIVO + IPI vs PEMBRO curve in the sensitivity analysis was more stable, following an initial steeper reduction in the hazard ratio between 0 and 6 months.

Figure 11: PFS hazard ratios–- NIVO + IPI versus all comparators – Sensitivity network–- Primary model

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; SoC, standard of care

3.4.2. Anchored MAIC

3.4.2.1. Definition

The anchored MAIC is another method of indirect comparison used to compare individual patient level data from one study (CM8HW) to aggregate data from another (KN-177), adjusting for differences in treatment effect modifiers between studies.

3.4.2.2. Transitivity and feasibility

Both anchored and unanchored MAICs were presented by the company, as scenario analyses, to validate the preferred use of the fractional polynomial NMA. The anchored MAIC used the population in KN-177 as aggregate data, to match against the IPD data from CM8HW, presenting treatment effects for chemotherapy, PEMBRO, and NIVO + IPI. The company identified seven treatment effect modifiers (age, ECOG PS, BRAF/KRAS/NRAS mutation status,

tumour sidedness, liver metastasis, liver or lung metastasis, and region) based on expert opinion of relevant baseline characteristics in mCRC. These were already similar pre-weighting (between trials differences ≤ 3%) for most variables. The EAG agreed with the robustness of methods used to determine treatment effect modifiers, and the clinical expert consulted by the EAG agreed with these. The company presented the effective sample size calculation, distribution of matching weights, and covariate balance plots, as expected for this ITC. Post-matching the groups were well matched and comparable. The ESS, upon matching, was 241.74, which was 79.79% of the original CM8HW sample – a good indication that the populations overlapped and were comparable. In addition to this, the mean propensity score weight was 1.000, with a range between 0.14 and 2.36. No extreme weights were evident.

3.4.2.3. Statistical methods

Post-weighting, the company presented methodology for fitting parametric survival curves using both quantitative (AIC and BIC) and qualitative (visual inspection) methods, as is standard practice. The company presented the generalised gamma parameterisations for all four treatment arms, and time varying hazard ratios and 95% confidence intervals for KN-177 and CM8HW between 0 and 180 months. The EAG believed the methods used were reasonable. The generalized gamma distribution allowed for a flexible fit to the data, though it did present a sub-optimal fit to observed PFS from CM8HW. See further discussion in 4.2.6.1.

3.4.2.4. Primary analysis results

An initial HR > 1 in both trials for NIVO + IPI, and PEMBRO vs. chemotherapy in the first months, suggested an initial higher risk of progression. Beyond this point, the HR remained below 1 up to the end of the measurement period (180 months). Within the first 24 months, the CIs did not overlap, indicating a significant difference in the HRs between the two trials, with NIVO + IPI yielding a lower HR and more favorable treatment effect. Beyond this point, the CIs overlapped and indicated no significant difference in treatment effects vs chemotherapy. From this model, the immunotherapy interventions could be interpreted to have broadly similar effects beyond 24 months, compared to chemotherapy.

The company present Table 14 summarising the HRs across ITC approaches, including the anchored MAIC NIVO + IPI vs. PEMBRO outcome. The EAG recognised that the PFS estimates for NIVO + IPI vs PEMBRO were overall dissimilar to the FPNMA. The result of the anchored MAIC was a slightly more conservative estimate of PFS compared to the FPNMA at 12 months, followed by a less conservative estimate of PFS at 24 months. Beyond this point the model

suggests a gradually worsening PFS up to 60 months, with the upper bound of the 95% CrI crossing one by 36 months. The model suggested NIVO + IPI is no more effective than PEMBRO beyond this time point. The EAG considered the differences between these findings as relating particularly to residual and unmeasured confounding, especially given that the FPNMA may be more effective at 'marginalising out' unmeasured confounding via a more flexible relative treatment effect function. In addition to this, the use of a parametric function (generalized gamma) that did not fully account for the observed shape of the hazard functions might have exacerbated differences between the two methods.

Table 14: NIVO + IPI versus PEMBRO PFS hazard ratios across ITC approaches

		HR (95% CrI) at month			
		12	24	36	48
FP NMA	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]
Anchored MAIC	NIVO + IPI vs PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]
Constant HR NMA	NIVO + IPI vs PEMBRO	[redacted]			

Abbreviations: CrI, credible interval; FP, fractional polynomial; IPI, ipilimumab; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NIVO, nivolumab; NMA, network meta-analysis; PEMBRO, pembrolizumab

These results did, however, show that the long-term treatment effect of NIVO + IPI, relative to PEMBRO, was sensitive to the methodology used within the ITC.

3.4.2.5. Sensitivity analysis results

The company presented an additional MAIC in the centrally confirmed population. However, this submission was flawed in that KN-177 PEMBRO data is in all randomised patients, not those with centrally confirmed MSI-H/dMMR status. The EAG considered this to violate the assumption of transitivity across the MAIC, and therefore the EAG did not interpret this analysis. Likewise, the company presented a sensitivity analysis using PFS per investigator alongside PFS per BICR. However, based on the response presented the EAG assumed that the company did not update the data for KN-177 in the PFS per investigator comparison, and this remained a concern.

3.4.3. Constant hazard NMA

The constant-hazard network meta-analysis was presented as another indirect treatment comparison scenario analysis for the primary endpoint. It was presented for completeness and as a validation exercise, noting that this should be interpreted with caution. The constant hazard NMA assumes that the hazard ratio between treatments remains constant over time, when comparing multiple treatments across various studies, using a common comparator. The appropriateness of this analysis relies on meeting the assumption of proportional hazards, which is violated, and therefore not appropriate for decision making. The EAG noted that hazards are not proportional across the 12-60-month follow-up period in either trial and that this had likely led to unrealistic PFS estimates. The constant hazard NMA provided a conservative estimate of the hazard ratio for NIVO + IPI vs PEMBRO, regardless of weighting strategy (weighted: [redacted]) and (unweighted: [redacted]). Compared to the FPNMA, the constant hazard NMA underestimated the likely benefit of NIVO + IPI across time points and was not appropriate for decision making. However, it did suggest caution when interpreting the FPNMA, in that it may be an optimistic estimate. Nevertheless, the EAG recognised the simplicity and transparency of the methods incorporated to run the constant hazard NMA, in spite of the data contravening the assumption of proportional hazards.

3.4.4. Adverse Events

The company presented log odds ratios for adverse events occurring in NIVO + IPI, vs PEMBRO and PAN + FOLFOX, estimated using simple indirect treatment comparison methods (Table 15). The company used fixed effects models for these comparisons, assuming a similar effect size across studies (KN177, CM8HW, PRIME). The EAG found the use of a fixed effects models in this scenario reasonable. The safety profile of NIVO + IPI vs. PEMBRO was not

significantly different overall. However, in the NIVO + IPI group, the odds of TRAEs of grade ≥3 were significantly greater, compared to PEMBRO, which was clinically plausible. Conversely, hypertension was significantly worse in the NIVO + IPI group. This finding was unexpected, as there was no obvious clinical reason for this discrepancy. Event numbers were, however, small.

NIVO + IPI demonstrated a better safety profile than chemotherapy on several outcomes, namely any AE grade ≥3, any TRAE, any TRAE grade ≥3, decreased neutrophil count, hypertension, asthenia, pneumonia, hyperthyroidism, diarrhoea, and neutropenia. This aligned with clinical advice to the EAG that NIVO + IPI would be expected to have an improved safety profile relative to standard chemotherapy but would be expected to be associated with more adverse events that PD-1 / PD-L1 monotherapy.

Table 15: Log odds ratios of incidence of any adverse event – fixed effects – primary network

	Log odds ratio (95% CrI)		CheckMate 8HW		KN-177	
Outcome	NIVO + IPI vs SOC (CheckMate 8HW)	NIVO + IPI vs PEMBRO (KN-177)	NIVO + IPI	SOC	PEMBRO	SOC
N			200	88	[redacted]	[redacted]
Any AE	[redacted]	[redacted]	197 (98.5%)	86 (97.7%)	[redacted]	[redacted]
Any AE grade ≥3	[redacted]	[redacted]	96 (48.0%)	59 (67.0%)	[redacted]	[redacted]
Any TRAE	[redacted]	[redacted]	160 (80.0%)	83 (94.3%)	[redacted]	[redacted]
Any TRAE grade ≥3	[redacted]	[redacted]	46 (23.0%)	42 (47.7%)	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CM, CheckMate; CrI, credible interval; IPI, ipilimumab; KN, KEYNOTE; NIVO, nivolumab; PAN, panitumumab; PEMBRO, pembrolizumab; SOC, standard of care; TRAE, treatment-related adverse event

The company presented a sensitivity analysis, limited to comparisons available from the PRIME study. PAN + FOLFOX had a significantly less favourable safety profile compared to NIVO + IPI for any adverse events grade ≥3, as well as for diarrhoea and neutropenia. Conversely, PEMBRO had a slightly more favourable safety profile compared to NIVO + IPI on the same outcomes, although this was not significant. Notably, compared to chemotherapy, NIVO + IPI had a significantly better safety profile for any adverse events grade ≥3 and for neutropenia incidence. NIVO + IPI also benefits from a better safety profile in terms of incidence of diarrhoea, although not significant.

3.5. Additional work on clinical effectiveness undertaken by the EAG

None.

3.6. Conclusions of the clinical effectiveness section

The EAG considered the company's SLR to be of reasonable quality and likely to have identified all key NIVO + IPI and comparator studies within the search remit. However, in the case of the company's FPNMA sensitivity analysis, the EAG noted the inclusion of one study – PRIME – with a broader population, not limited to dMMR/MSI-H – which was consequently not identified through the company's SLR.

The EAG generally considered CM8HW to be a well-conducted RCT, although noted a risk of performance and detection bias since the trial was open label. CM8HW is an ongoing trial, so only interim rather than final results were available, and not for all outcome measures. To supplement evidence from CM8HW, the company also presented clinical evidence from Cohort 3 of CM142, a single-arm Phase 2 trial of NIVO + IPI, which had a longer available period of follow-up and available OS data. The EAG noted that there was considerable crossover (n=[redacted] from chemotherapy to NIVO + IPI as a result of disease progression in CM8HW. However, while a challenge for interpretation, the EAG was satisfied that the crossover does not represent a deviation from available UK treatments, as NIVO + IPI is available as a subsequent treatment in current UK practice.

The primary endpoint in CM8HW is PFS per BICR. The EAG was satisfied that NIVO + IPI showed a PFS advantage over chemotherapy, HR 0.32, 95% CI 0.23, 0.46), using this definition. Among those receiving chemotherapy in the control arm, 66 (75.0%) patients received targeted therapies, with 56 (63.6%) receiving bevacizumab and 10 (11.4%) receiving cetuximab. Treatment with FOLFOXIRI and capecitabine were not allowed according to study

protocol. Since bevacizumab is not used in this indication in England, the company conducted a subgroup analysis by chemotherapy regimen and found that PFS was [redacted] in bevacizumab-containing than cetuximab-containing regimens. By assuming that UK chemotherapy reflects chemotherapy in CM8HW, the company was making a conservative assumption. Using data from CM142, at 60 months, the OS rate was 67%.

Direct head-to-head evidence for NIVO + IPI versus PEMBRO was not available. The company presented a FPNMA alongside three validating scenario analyses. In lieu of the proportional hazards assumption not being met, and the level of evidence available, the FPNMA was an appropriate analysis for this data. Not least because the FPNMA permitted a flexible fit, allowing the baseline hazard function and relative treatment effect (the hazard ratio) to vary over time. The EAG noted the robustness of the methods used in the conduct of the FPNMA. However, the long-term treatment effect of NIVO + IPI relative to PEMBRO was sensitive to the methodology used within the ITC and estimates from the proportional hazards NMA (validating scenario) indicated that the FPNMA may be optimistic overall.

The EAG generally agreed that the clinical evidence base supported a benefit for NIVO + IPI over chemotherapy (direct evidence) and PEMBRO (indirect evidence). However, the EAG identified two key issues in the clinical effectiveness evidence, which should be taken into account when interpreting these findings.

First, OS data from CM8HW were not presented in the CS. OS is the endpoint listed first on the NICE scope and is important to inform / validate the economic model. The company said that it had not yet been supplied OS data form the pivotal trial by its vendor as the prespecified number of events had not yet been reached . The EAG advised that it was aware that the data would not be mature and would be treated as such, but that provision of these data was essential to enable appropriate model validation. The EAG noted that at the time of the interim analysis (12 October 2023), the information fraction was 80%, suggesting that OS data at this point in time would likely closely parallel the final OS data. The company justified its position based on precedent from prior appraisals and on the hierarchical statistical testing strategy pre-specified in the trial protocol and to “preserve the trial’s integrity and to avoid introducing bias that could potentially lead to inaccurate conclusions”. The EAG also noted that death data is available (as this is a safety endpoint) and that in 3 of the 5 example TAs quoted by the company OS data was supplied before the Committee made a decision; the remaining two were in the adjuvant space were surrogacy between DFS and OS can be considered more intuitive

given the potentially curative nature of surgery. The EAG considered that the production of an ad hoc confidential analysis for regulatory and decision-making purposes would be standard and that the company's decision not to do this is a major issue for the appraisal. The surrogacy of OS, as determined by PFS, was based on the post-hoc correlation between PFS and OS from cohort 3 (1L NIVO + IPI) in the CM142 trial (n=45, median follow-up 52.6 months). Patient-level correlations between OS and PFS ranged from r=0.82 to r=0.95 (Spearman's rho correlation). However, this analysis did not demonstrate that the assumption made in later economic analysis that gains in TTP will directly translate to gains in OS is reasonable. Overall, conclusions regarding OS had very limited interpretability, and the EAG were limited in the appraisal of the usefulness of PFS as a surrogate. The EAG noted that there were 44 deaths on the NIVO + IPI arm (22%) and 37 deaths on the chemotherapy arm (42%); whilst these data are immature there was enough information available to be able to provide some validation. The initial datacut of KN-177 had 56 deaths in the PEMBRO arm (37%) versus 69 in the chemotherapy arm (45%) indicating that there may be some advantage in OS for NIVO + IPI. However, without KM data this information was difficult to interpret. The EAG considered this a resolvable uncertainty.

Second, the EAG had concerns about the transitivity of the NMA network. Transitivity of the network relies on the generalisability of centrally vs. locally tested microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) status between the trials. In KN-177, dMMR/ MSI-H status was locally confirmed and therefore it was appropriate to compare all randomised patients in the ITC. Nevertheless, the EAG considered the use of central testing important for preventing non-differential ascertainment bias. Unfortunately, central testing was not performed in KN-177 which prevented a robust like-for-like comparison from being carried out. Furthermore, transitivity of the network relied on the class treatment effect, resulting from the control arms. The EAG stressed that the heterogeneity within the comparator groups adds a level of uncertainty to the estimate. The company presented evidence that within the chemotherapy arms of CM8HW and KN-177, they were similar enough for comparison. Yet some heterogeneity in outcomes may be explained by the percentage of patients receiving bevacizumab (CM8HW = 64% vs. KN-177 = 70%), which is not used in UK practice. This added a level of uncertainty to the estimates produced by the FP NMA. The EAG considered this an unresolvable uncertainty, as there is no possibility of central testing in KN177.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The EAG offers commentary below on the company's reviews of cost-effectiveness evidence, which the company presents in Appendix G of the CS. Generally, the review of cost-effectiveness was not as well reported as the clinical SLR. This means it was not possible for the EAG to assess whether the cost-effectiveness review is as well conducted and what the implications of this may be for the economic evidence base.

Table 16: Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix G 1.2-1.5	The choice of databases to search was reasonable. However, compared to the company's clinical search, the economic searches were poor. Just one line was used to describe the population of interest in the Medline search. No MeSH terms were used. The Embase search was better constructed and included the use of EMTREE terms. However, in neither case were the study type filters used cited. The clinical search was for dMMR/MSI-H, but the economic search population was for recurrent or metastatic CRC. The company clarified that this was purposely done to identify a broader literature for the economic review.
Inclusion criteria	Appendix G 1.7	The inclusion criteria for the cost-effectiveness review are broader than the clinical review. They encompass mCRC at all lines of treatment. This broader approach is fairly typical of cost effectiveness reviews and the EAG considered it appropriate.
Screening	Appendix G 1.8	Study selection was conducted independently by two reviewers with the use of consensus or involvement of a third reviewer to resolve any discrepancies. The EAG considered this to be appropriate.
Data extraction	Appendix G 1.9	Data extraction was conducted by one reviewer and quality checked against the original source. While this is not the gold standard independent dual review, the EAG considered it to be broadly appropriate.
QA of included studies	Appendix G 3	Risk of bias assessment of included studies was conducted using the Drummond-36 checklist. It was conducted by one reviewer and validated by a second reviewer. The EAG considered this to be broadly appropriate.

Abbreviations: CRC, colorectal cancer; CS, Company Submission; dMMR, DNA mismatch repair deficient; EAG, External Assessment Group; HRQoL, health-related quality of life; MSI-H, microsatellite instability high; QA, quality assessment

Table 17: Summary of EAG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix H 1.1-6	The choice of databases to search was reasonable. However, compared to the company's clinical search, the economic searches were poor. Just one line was used to describe the population of interest in the Medline search. No MeSH terms were used. The Embase search was better constructed and included the use of EMTREE terms. However, in neither case were the study type filters used cited. The clinical search was for dMMR/MSI-H, but the economic search population was for recurrent or metastatic CRC. The company clarified that this was purposely done to identify a broader literature for the economic review. There was a minor error in the search strategy as lines 25 to 27 in the Embase search strategy are not included in the final search. This is probably due to an error in line 32 ("or/28-31" is probably meant to be "or/27-31"). This meant that pre-2019 conference abstracts were not NOT'ed out of the search, although the later date restriction line (for all search results) will have removed them anyway. The population terms in the CENTRAL search are all hyphenated (e.g. metastatic-colorectal-carcinoma). This may be a transcription error. But if the search was run this way, then while CENTRAL does still return results, it will have returned fewer hits than if the search terms were not hyphenated.
Inclusion criteria	Appendix H 1.7	The EAG considered the inclusion criteria to be broadly appropriate, although it was noted that surrogate populations, including the general public and health professionals, were included for obtaining utility values.
Screening	Appendix H 1.8	Screening was conducted by two reviewers with any discrepancies resolved through consensus or the involvement of a third reviewer. The EAG considered this appropriate.
Data extraction	Appendix H 1.9	Data extraction was conducted by one reviewer and checked against the original source by a second reviewer. Any discrepancies were resolved through discussion. While this was not the gold standard independent dual data extraction, the EAG considered it broadly appropriate.
QA of included studies	Appendix H 2.2.1	Only informal quality assessment was presented.

Abbreviations: CRC, colorectal cancer; CS, Company Submission; dMMR, DNA mismatch repair deficient; EAG, External Assessment Group; HRQoL, health-related quality of life; MSI-H, microsatellite instability high; QA, quality assessment

Table 18. Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix I.1.1-6	The choice of databases to search was reasonable. However, compared to the company's clinical search, the economic searches were poor. Just one line was used to describe the population of interest in the Medline search. No MeSH terms were used. The Embase search was better constructed and included the use of EMTREE terms. However, in neither case were the study type filters used cited. The clinical search was for dMMR/MSI-H, but the economic search population was for recurrent or metastatic CRC. The company clarified that this was purposely done to identify a broader literature for the economic review.
Inclusion criteria	Appendix I.1.7	A broad mCRC population was considered, alongside a dMMR/MSI-H sub-population, which the EAG considered appropriate. An appropriately broad range of resource use and cost use parameters was considered.
Screening	Appendix I.1.8	Screening was conducted by two independent reviewers. Any discrepancies were resolved by consensus or the involvement of a third reviewer. The EAG considered this appropriate.
Data extraction	Appendix I.1.9	Data extraction was conducted by one reviewer and quality checked against the original source by a second reviewer. Any discrepancies were resolved by discussion. While not the gold standard independent dual review, the EAG considered this broadly appropriate.
QA of included studies	-	Not discussed.

Abbreviations: CRC, colorectal cancer; CS, Company Submission; dMMR, DNA mismatch repair deficient; EAG, External Assessment Group; HRQoL, health-related quality of life; MSI-H, microsatellite instability high; QA, quality assessment

The CS identified 19 relevant economic evaluations. The two of these the EAG considers to be of most relevance are TA709: the first-line NICE appraisal of pembrolizumab (the comparator used most frequently in the first-line setting) and TA716: the NICE appraisal of nivolumab with ipilimumab for metastatic MSI-H/dMMR colorectal cancer after fluoropyrimidine-based combination chemotherapy. It is noteworthy that TA709 was conducted before nivolumab with ipilimumab was recommended as a treatment for previously treated patients and therefore the results for the chemotherapy comparator should be interpreted with caution as they do not reflect the current treatment pathway. The same is true for SMC2375.

The CS identified 17 relevant studies containing utility data and 20 relevant studies of cost and HCRU. Again, the most relevant data are from previous submissions. Unfortunately, the company redacted the utility data from its own submission in the previously treated setting.

4.2. Summary and critique of company's submitted economic evaluation by the EAG

The company initially submitted three economic model files. One for adults, one for adolescents and one for a weighted population. Following confirmation of the proposed indication only the adult model was relevant. At clarification question response the company submitted a further seven model files for the adult population over a week late (one for each scenario) and following the EAG noting an error in the company model the company then supplied a further 54 model files the week the EAG report was originally due (one for each scenario analysis conducted by the company).

The EAG noted that submitting over 60 Excel files is completely unwarranted. Good practice would be to submit one model for the indication with switches to allow different scenarios to be run. The proliferation of submitted models, despite EAG request for one model containing all the information, required the EAG to make substantial amends to the company's Excel files to produce a starting model to which EAG analyses could be added. This has resulted in considerable extra resource use for the EAG and limited our ability to conduct adequate quality control.

4.2.1. NICE reference case checklist

Table 19: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate and captured the health benefit to patients. The outcomes of carers were not captured which is considered appropriate given these were not included in other appraisals in this disease area
Perspective on costs	NHS and PSS	NHS and PSS as appropriate
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost–utility analysis with fully incremental analysis as appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	40 years; this is long enough for the adult population (mean age 60.9, <1% remaining alive in the last model cycle). Scenario analysis provided with 85.5 year time horizon which is considered long enough.

Attribute	Reference case	EAG comment on company's submission
Synthesis of evidence on health effects	Based on systematic review	Effectiveness (TTP) based on ITC of PFS using data identified via systematic review. PrePS based on assumption only. Data used for PPS not identified via systematic review and applied in a manner that has major face validity issues. AEs naively extracted from studies identified via systematic review. Utilities based on CM8HW. Data from systematic review not synthesised. Use of alternative sources tested in scenario analysis with limited ICER impact.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Expressed in QALYs. EQ-5D-3L used.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Reported directly by patients. Completion rate higher in the NIVO + IPI arm and relatively few observations post-progression ([redacted]).
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	As confirmed during clarification, the UK tariff (Dolan, 1997) was used for the EQ-5D.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Per the NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs were primarily based on NHS reference costs 2021 - 2022[25] as appropriate
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and QALYs were discounted at 3.5%.

Abbreviations: EQ-5D, EuroQol 5 dimensions; HRQoL: health-related quality of life; NHS, National Health Service; IPI, ipilimumab; NICE, National Institute for Health and Care Excellence; NIVO, nivolumab; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal; TTP, time-to-progression

4.2.2. Model structure

The company used a state transition structure with states based upon progression status at first-line. This aligns with TA709 and would appear reasonable given that immaturity of OS data prevents direct extrapolation of survival and the need to account for differential availability of

subsequent treatments across arms. This method does not model survival endpoints independently, but rather focusses on estimating the structural relationship between PFS and OS in the trial data which has the benefit of reflecting clinical expectation and the limited available data on surrogacy between OS and PFS (see Section 3.2.2.5 for full critique) that progression will impact on survival expectations.

Time-dependency for transitions from progression to death was incorporated using a VBA-equivalent of tunnel states within the economic model. The EAG has checked these calculations and they appear to function as expected.

The model uses the following data to inform transition probabilities:

- On to off treatment in PF: CM8HW Kaplan Meier data for NIVO + IPI and chemotherapy; naïve assumption of equivalence between NIVO + IPI and PEMBRO
- PF to PD: CM8HW for NIVO + IPI and chemotherapy, PFS ITC for PEMBRO
- PF to death (PrePS): general poulation mortality and CM142 data in scenario analysis due to lack of data from CM8HW
- PD to death (PostPS): CM142 PPS data – assumed equal for all model arms in the base case; scenario analysis presented using CM142 Cohort 2 OS data post chemotherapy

There are a number of recommendations within TSD19[26] which were not followed within the implementation of the state transition approach:

- Transition probabilities within state transition models should be estimated using appropriate statistical methods and reflect all relevant evidence – evidence has not been identified using systematic methods and in the company base case only PPS data from CM142 NIVO + IPI cohorts is currently used.
- State transition modelling should be used alongside the PartSA approach to assist in verifying the plausibility of PartSA's extrapolations and to address uncertainties in the extrapolation period, even if this is only plausible for the pivotal trial - model predictions are not validated against OS data from CM8HW which the company has not provided. This represents a major omission.

- Presentation of results from all PartSA and state transition models should include tabulations showing the states in which life year and QALY differences between interventions accrue and a justification of why these differences should be considered plausible – the plausibiity of differences in PFS and PPS is not assessed

The EAG described its key concerns with the assumptions made within the model structure and data sources chosen to populate the model in the sections below.

4.2.2.1. How treatment effect is incorporated within the model

The EAG noted that within this model structure gains in PFS directly equate to a gain in the estimated OS. Given this, the use of CM142 PPS data in the base case to represent PostPS for all treatments represented a major issue as the subsequent therapies available differ between arms. Patients receiving chemotherapy were able to receive NIVO + IPI as a second line treatment which has greater effectiveness than other available options as per TA716. Inclusion of only the additional cost of receiving NIVO + IPI as a subsequent treatment and not the impact on effectiveness was a major omission which biases in favour of NIVO + IPI. The company provided scenario analysis in response to clarification questions which sought to address this issue.

The EAG also noted that there was no evidence that gains experienced in PFS would directly translate to gains in OS; this is particularly uncertain in the comparison to PEMBRO. As OS data were not provided from CM8HW the EAG was unable to validate this assumption in any meaningful way. As such the EAG presented scenario analysis assuming equal OS between NIVO + IPI and PEMBRO which, without alternative data being presented, the EAG considered to be equally plausible.

4.2.2.2. Incorporation of time on treatment

The assumption that time to discontinuation (TTD) is the same between NIVO + IPI and PEMBRO whilst effectiveness in terms of TTP is increased for NIVO + IPI biases in favour of NIVO + IPI and was not supported by the available data as, although a naïve comparison of these two arms indicates similar TTD, TTD is longer in the chemotherapy arm of KN-177 than in CM8HW. No scenario analyses were offered by the company to address this issue.

4.2.2.3. Transitions from progression-free

The use of the PFS ITC to apply to TTP followed by the assumption that all treatments have the same PrePS createed some bias in the analysis as the PFS ITC includes both transitions. This, together with the absence of an OS-based ITC, or indeed of OS data from CM8HW, to compare with PrePS, precluded assessment of bias. The majority of PFS events during both the CM8HW and KN-177 studies were progression events. Death (as opposed to progression) events in patients with a PFS event occured in [redacted] of the NIVO + IPI arm and [redacted] of the chemotherapy arm in CM8HW (data supplied by company at factual accuracy check) and 20.7% of the PEMBRO arm and 23.9% in the chemotherapy arm after median follow-up of 28.4 months in KN177 in the ITT populations of the two trials.[27] This indicated that the assumption that the same treatment effect would be observed for PFS and TTP was likely reasonable.

The EAG were unclear as to why the company did not calculate PrePS based on the difference between TTP and PFS as was the case in TA709 as this would appear to require considerably fewer assumptions. Response to clarification questions (D1) did not enlighten the EAG further on this point but it did appear to indicate that the bias introduced favoured the chemotherapy arm – at least in the first year. Impacts in the longer-term were unclear but were likely to favour NIVO + IPI as more patients remain progression free. Comparison of observed PFS and modelled PFS showed a small overestimation (of a similar size [redacted] in both arms at 2 years. Scenario analysis using CM142 data showed that curves fitted to observed PrePS crossed general population mortality around 5 years. The impact was therefore likely to be relatively limited (Figure 14).

4.2.2.4. Receipt of subsequent treatment

The company assumed that subsequent treatment was received whilst in the progressive disease state which aligned with clinical practice but did not align with the definition of PFS chosen to be used from the clinical trial data, where patients who received a subsequent treatment without a prior scan to confirm RECIST-assessed progression were censored rather than classed as having had a progression event. Though there was a systematic difference between arms in CM8HW in the percentage of patients censored due to subsequent treatment ([redacted] in NIVO + IPI vs [redacted] for chemotherapy, including [redacted] vs [redacted] censored for subsequent systemic treatment specifically), it does not appear that the HR estimated for PFS not including censoring at point of subsequent treatment was systematically different (HR of [redacted] defining receipt of subsequent treatment as an event, versus 0.32 (95%

CI: 0.23, 0.46) for the primary definition). However, this did not preclude the possibility of bias being carried 'through the network' in a subsequent ITC using results from KN-177.

Finally, the method the company used to apply subsequent treatment costs is flawed and did not appropriately account for the stopping rule for NIVO + IPI and PEMBRO in second line (see Section 4.2.8.2 for further detail).

4.2.2.5. Cycle length

The model uses a 28 day cycle length with the justification provided being that this aligns with the frequency of scans during longer-term follow-up in the CM8HW trial (post 24 weeks), better alignment with oncology follow-up (2 weekly), disease monitoring (1-4 monthly) and that it may better reflect wastage for oral treatments. Whilst the EAG did not fully agree with the logic (high cost treatments included are given as injections and as the company note initial oncology follow-up is more frequent) it do not consider this to be a major issue likely to impact on the results. Half-cycle correction has been applied, which is correct for the majority of costs and outcomes but not appropriate for the cost of injectable drugs, which should be incurred at the time received. The EAG noted the method used to apply half cycle correct will underestimate the cost of treatment as not all patients receive the first dose of drug.

4.2.3. Population

This cost-effectiveness analysis assessed NIVO + IPI for the treatment of previously untreated patients aged 18 years and over with dMMR/MSI-H mCRC, in line with the anticipated licensed indication.

The population was modelled using demographic data from CM8HW (see CS Table 52 for values used). The company also supplied information for a weighted mean population, this should however be ignored and instead the weighted average of the cost and QALY outcomes should be used to calculate the outcome for the overall population. This was provided as a scenario analysis during clarification (see clarification response Table 14).

Clinical expert advice to the EAG was that the characteristics of the CM8HW trial were broadly reflective of what would be expected in practice, aside from the weight of trial participants [redacted] which was lower than would be expected in practice given mCRC patients would be expected to have a similar weight to the general population (Section 3.2.2.2). The company provided scenario analysis in response to clarification questions using general population weight data which the EAG consider to be more appropriate.

4.2.4. Interventions and comparators

PEMBRO can be considered the key comparator as, based on advice received by the EAG, this is the treatment most commonly used in practice with patients eligible for treatment with immune-oncology with the relevant diagnostic tests conducted to identify dMMR/MSI-H. Such patients typically receive this treatment in the vast majority of cases.

Other relevant comparator treatments, which are available for the full patient population and were used prior to the NICE recommendation for pembrolizumab, include FOLFOX, FOLFIRI and FOLFOXIRI. CAPOX is also available but was not noted as part of standard practice by the clinical expert consulted by the EAG. Patients with (EGFR)-expressing, RAS wild-type disease are also eligible for panitumumab-based therapy or cetuximab-based therapy which is preferred over doublet or triplet chemotherapy alone; these two options were found in a prior NICE appraisal to have similar effectiveness.[29] Clinical experts consulted by the EAG agreed with the conclusion of TA709[29] that capecitabine is only used in patients who are too frail to receive the alternatives and is therefore not a relevant comparator. They also considered FOLFOX and FOLFIRI to have similar effectiveness in line with TA709 with limited benefit of the triplet combination which is predominantly used in younger patients with the intent of reducing tumor size prior to enable surgery with curative intent due to increased response rates relative to treatment with doublet chemotherapy.

The company assumed that the effectiveness demonstrated in the CM8HW trial was applicable to the effectiveness that would be expected with the mix of chemotherapy treatments received in clinical practice.

According to the CS (page 67), of those treated in the chemotherapy arm (n = 88), 66 (75.0%) patients received targeted therapies, with 56 (63.6%) receiving bevacizumab and 10 (11.4%) receiving cetuximab. 51 (58.0%) received oxaliplatin-containing regimens (mFOLFOX6), and 37 (42.0%) received irinotecan-containing regimens (FOLFIRI). Treatment with FOLFOXIRI and capecitabine were not allowed according to study protocol.

The proportion receiving a targeted therapy in the CM8HW trial (75%) was considerably higher than ad-board opinion received by the company would expect (7.5%; CS Table 82). Internationally bevacizumab is frequently used in combination with standard chemotherapy which is not allowed in the UK. The issue of a high proportion receiving bevacizumab in the comparator arm of the trial was also present in the pembrolizumab appraisal (TA709). In TA709

bevacizumab was considered likely to offer a small benefit to patients over standard chemotherapy, so the trial may underestimate the relative effect of NIVO + IPI compared with standard care. The company in TA709 assumed that patients who received bevacizumab in KN-177 would instead receive cetuximab in practice, however, cetuximab is only available to patients with RAS wild-type disease. Of the patients whose mutation status was known in CM8HW 67% were RAS wild-type (146/217); this is the maximum proportion that would be able to receive a targeted therapy in clinical practice indicating that the outcomes observed on the comparator arm of the CM8HW are unlikely to meaningfully overestimate what would be expected to be observed in practice.

4.2.5. Perspective, time horizon and discounting

The model takes an NHS and PSS perspective, in line with the NICE reference case. 40 years; this is long enough for the adult population (mean age 60.9). The model discounts both costs and outcomes at 3.5%, again in line with the NICE reference case.

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Progression-free to progressed disease

General approach

TTP data was extrapolated from CM8HW for NIVO + IPI and chemotherapy. The Kaplan-Meier curves for the two treatments cross at around 4 months and after this timepoint diverge with clear violation of the proportional hazards assumption. A U-shaped curve was observed on the Schoenfeld residuals plot (CS Figure 33) with the hazards initially diverging and then converging again in the longer term. No events were observed on the chemotherapy arm after 16 months, at which point less than 20 of the initial 101 remained at risk. This could be an artefact of low patient numbers or it could indicate that these patients responded sufficiently to qualify for curative surgery or local ablation [redacted] of patients on the chemotherapy arm received surgery and [redacted] radiotherapy based on the CSR Table 6.5.4-1). The EAG noted that the TTNT KMs presented by the company in response to clarification questions (C1) showed a consistent decline towards zero for both trial arms, indicating that the majority of patients are likely to require a subsequent treatment of some type (unfortunately what was classed a subsequent treatment for this analysis is not detailed).

The company fit independent standard parametric curves per TSD14.[30] The CS stated that identification of the best model fit was based on the model selection algorithm outlined in

Palmer et al., (2023)[31] and that selections were validated by clinical experts during advisory board meetings. No details of these meetings were provided and this type of validation is not recommended in the NICE manual 2022 due to the biases inherent; instead structured expert elicitation of survival at landmark timepoints would be preferred as a more robust way of incorporating information from experts.[32,33] The Palmer algorithm suggests for a trial with 2 arms the following steps:

1. Assess PH assumption via log-cumulative hazard plots, scaled Schoenfeld residual plots, Grambsch-Therneau test, Royston-Parmar augmented log-rank test – the first 2 of these are presented which is considered reasonable
2. Elicit expert beliefs focussing on the shape of the long-term hazard functions and the potential for substantial survival heterogeneity between arms – not conducted
3. Consider observed and potential future turning points – not conducted
4. Make a formal decision on whether flexible survival modelling is required – not conducted

As can be seen above there is no evidence of any of the steps suggested being followed after the assessment of the PH assumption.

The model does not allow the use of the FP NMA to model outcomes for NIVO + IPI despite requests for this functionality from the EAG on the clarification call. This means that outcomes are modelled using a different framework for PEMBRO and NIVO + IPI, which is not ideal.

NIVO + IPI

The company selected the generalised gamma for NIVO + IPI on the basis of it having the lowest AIC, input from the advisory board and consideration that the extrapolation validated reasonably well against TTP from CM142, PFS from KN-177 using landmark survival and restricted mean survival time and limited comparison with other published literature sources.

Figure 12 demonstrates the considerable uncertainty associated with the curve fit. The generalised gamma curve does not provide a good fit to the observed trial data (see CS Figure 35); none of the other standard parametric curves provide an improved fit as all initially overestimate compared to the Kaplan Meier data and then underestimate in the middle portion. This indicates that a more flexible curve fit able to capture the more complex shape of the hazard function is worth exploration. In response to clarification questions, the company presented a series of one-knot and two-knot splines incorporating hazard, odds and normal

functions. Of note is that the two-knot odds function spline emerged as having the lowest AIC and BIC for NIVO + IPI. Though all fits were broadly similar within the trial period, both the two-knot odds spline and the two-knot normal spline generated a substantially worse survivor function for time to progression beyond the trial period. It should be noted that at 5 years the two-knot odds spline validates equally well against observed TTP in CM142 but results in a very different long-term outlook and estimate of median TTP ([redacted]).

Table 20: Comparison of model fit to longer term data for NIVO + IPI TTP

	Median, years (95% CI)	1-year	2-years	5-years
CM8HW observed	[redacted]	[redacted]	[redacted]	[redacted]
CM142 Cohort 2 observed	[redacted]	[redacted]	[redacted]	[redacted]
CM142 Cohort 3 observed	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Two-knot odds function spline	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ipi, ipilimumab; NIVO, nivolumab; TTP, time-to-progression

Source: Table 15

Clarification question response and data taken from the economic model for the two-knot odds function spline

Clinical validation was initially provided comparing TTP and PFS which the company acknowledge cannot be considered interchangeable; the rationale for this was unclear as the company have access to IPD to CM142 which is used within the validation exercise subsequently provided. In response to clarification, the company provided clinical validation against TTP from CM142, which closely matched landmark estimates at one-year, two-year and five-year points (Table 20).

It should be noted that there are differences between the CM142 trial and CM8HW which impact on the usefulness of this trial for validation:

- CM142 allowed reinitiation – impact unclear; would result in improved OS
- The dose of NIVO + IPI used in CM142 is different (IPI is given 6 weekly rather than 3 weekly) – expected minimal impact

- CM142 included more US/European patients, CM142 did not include participants with ECOG 2 and the proportion of participants with Lynch syndrome was moderately higher – expected minimal impact

Clinical expert advice to the EAG was that the generalised gamma was probably reasonable as patients who respond to treatment with IOs and relapse usually happens within the 2 years of treatment or shortly after if it is going to happen.

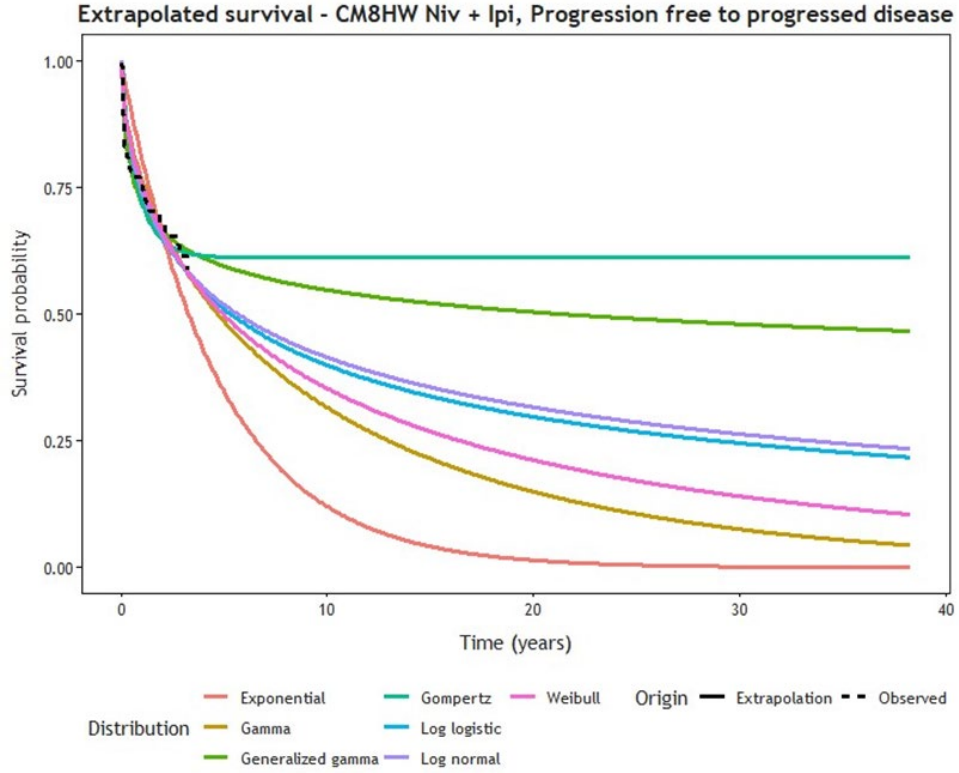
Chemotherapy

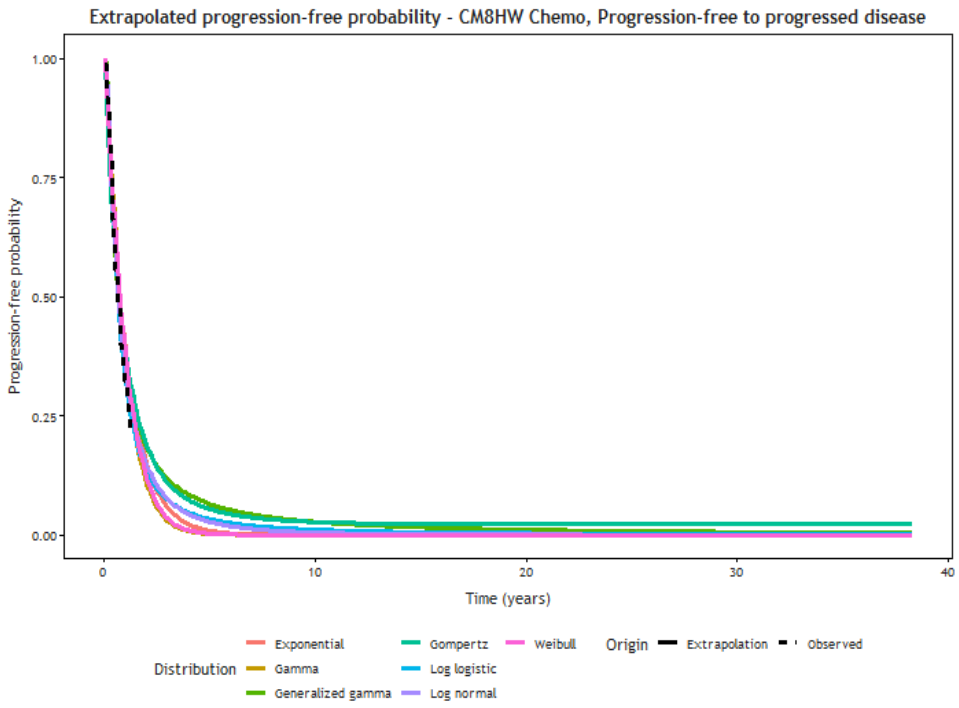
The generalised gamma was also selected for the base case for the chemotherapy arm for consistency with the selection with the NIVO + IPI arm and as this was the more optimistic of the three best fitting curves according to statistical fit. Again there were issues with the fit to the observed Kaplan Meier data, with initial underestimation followed by overestimation in the middle of the dataset. The EAG also suspected the Kaplan Meier has not been reproduced correctly as the plateau observed in TTP in CS Figure 32 is missing from the later figures e.g. CS Figure 37 and 38 which only present KM data for just over a year (compared to 30 months of observed data), if this had been included in the graphic then the EAG anticipated that longer term TTP would be underestimated.

Validation for chemotherapy was conducted primarily versus KN-177 as no alternative source of long-term landmark estimates was identified. The generalised gamma provides the closest fit to the data observed in KN-177 and the 95% CI of all 3-year CM8HW extrapolations encompass the estimated 3-year PFS from KN-177. The 2 knot odds spline fit considered to be the most suitable spline fit for NIVO + IPI provides a somewhat higher estimate of long-term PFS than the generalised gamma for the chemotherapy arm ([redacted] remaining progression free at 5 years vs [redacted]) with all of the spline fits having similar statistical goodness of fit and all of them being an improvement on the generalised gamma model.

Clinical expert advice to the EAG was that the chemotherapy group would be expected to have a much shorted TTP than NIVO + IPI as patients do not respond well to chemotherapy and any response is short-lived. All the curves presented were considered to be similarly reasonable.

Figure 12: Extrapolated survival from CM8HW





Abbreviations: ipi, ipilimumab; Niv, nivolumab

Source: replicated from CS Figure 36 and Figure 38

Pembrolizumab

As no direct evidence was available for pembrolizumab TTP outcomes were extrapolated using the FP NMA for PFS applied to TTP in the base case; assuming the HR between treatments for PFS was approximately comparator to the HR for TTP. The impact of using alternative estimates from the anchored and non-anchored MAICs and HR-based NMA are used as scenario analyses. The un-anchored MAIC was not considered suitable for decision-making and is therefore not considered within EAG scenario analysis. The EAG agreed with use of the FP NMA in the model base case (see Section 3.4 for further critique of the ITCs).

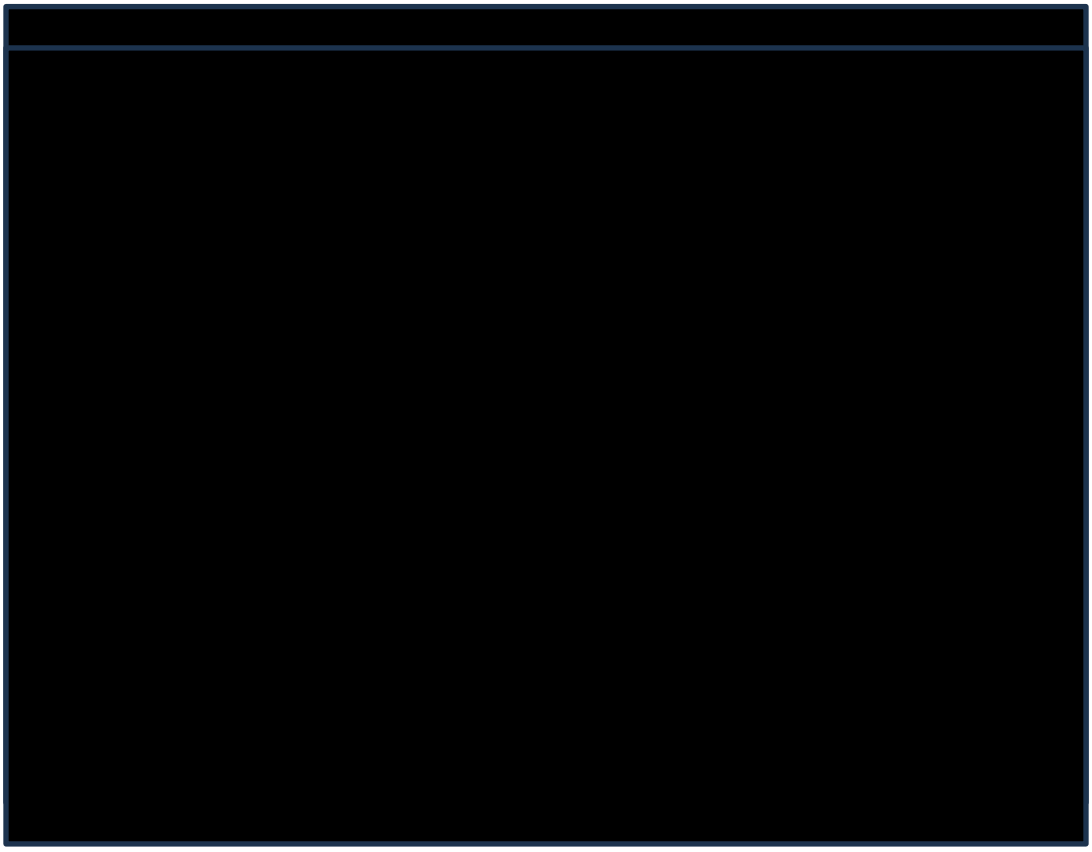
The company were asked to supply data from CM8-HW for NIVO monotherapy to validate the projections for PEMBRO. Unfortunately, this was not possible at this however, the EAG note these data may be available before the planned Committee meeting given the estimated timing of late Q4 2024 (CQ A15). Data was supplied for CM142 cohort 1, however (Appendix O).

Implications for treatment effect

The model applied each survival curve / the FP NMA for the full model time horizon. The potential for treatment effect waning was not explored. The company justified this on the basis that: “post-progression survival is based on CM142 and incorporates the impact of treatment switching.” This is not an adequate justification as by definition TTP only looks at the treatment effect prior to progression.

Figure 13 demonstrates the modelled treatment effect for TTP; it can be seen that the treatment effect vs PEMBRO reduces over time but remains positive for the entire modelled horizon meaning that the gap between survival curves continues to increase. Clinical expert advice to the EAG was that whilst an initial higher response rate is expected this is usually seen in the first year of treatment; it would not be expected that benefit would continue to increase. Similarly progression is usually observed within the first 2 years of shortly after. Given this advice and the sensitivity to FP NMA fit selection described in Section 3.4 the EAG assumed hazards for NIVO + IPI and PEMBRO were equal after two years in its base case. This reflected the clinical advice received and is a time point and which reasonable numbers remain at risk in the NIVO + IPI arm of the CM8HW trial. The EAG tested the impact of setting the hazards equal at one year in scenario analysis.

Figure 13: Modelled treatment effect for TTP



Abbreviations: IPI, ipilimumab; NIVO, nivolumab; TTP, time-to-progression
Source: EAG plot based upon data in the Patient Distribution sheet in the model

4.2.6.2. Progression free to death

The company assumed that PrePS is equal to general population mortality. The EAG considered this to be flawed as data from both CM-8HW and KN-177 demonstrate a reasonable proportion of patients experiencing a death event as part of PFS early on in the trial [redacted] - 23.9%. The company presented a scenario analysis using data from CM142 (Figure 14) which the EAG considered to be reasonable but a less ideal approach than calculating PrePS based on the difference between the PFS and TTP curves from CM8HW.

Figure 14: Comparison of CM142 PrePS and general population mortality

Abbreviation: PrePS, PF to death
Source: Produced using the company economic model

4.2.6.3. Validity of predicted PFS

Figure 15 compares PFS observed in CM142 (digitised from CSR for Cohort 3 NIVO + IPI, from Appendix O for Cohort 1 NIVO mono and from Doc B ITT population for CM8HW) with modelled PFS. The model predictions for PEMBRO mirror the CM142 data for NIVO mono in the first year after which time the model appears to somewhat underpredict. This indicates that there is a systematic bias in favour of NIVO + IPI in the comparison versus PEMBRO. The model predicts observed PFS well in CM8HW for NIVO + IPI but overpredicts observed PFS for chemotherapy after 6 months. This indicates some bias in favour of chemotherapy in that comparison.

Figure 15: Comparison of observed to modelled PFS

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; PFS, progression-free survival

4.2.6.4. Progressed disease to death

As data from CM8HW were not sufficiently mature the company use data from CM142 instead. The company did not present any search to identify suitable data to estimate probabilities for

this transition and the EAG are aware of other sources (e.g. KN-177) which have not been considered. On the face of it, though, use of data from CM142 is considered reasonable.

Company base case – assumption of equal PPS

The company in their base case combine data from CM142 Cohort 2 (2L+ NIVO + IPI) and 3 (1L NIVO+ IPI) who had experienced a progression event. The sample size for the combined cohort was relatively small, leading to uncertainty in the predictions (n=57). Patients receiving subsequent treatment in CM142 could reasonably be expected to represent those who are receiving chemotherapy as a subsequent treatment after NIVO + IPI or PEMBRO (see Section 4.2.8.2) although there may be some minor differences which could impact on outcomes:

- By combining outcomes across the cohorts the company included patients at 3L+ as well as 2L. Figure 5 of Appendix O, however, demonstrates similar PPS across the cohorts and therefore the EAG do not consider this to have a large impact.
- There were some issues with the doses in these studies not reflecting the expected dose for 1L NIVO + IPI. However, clinical expert advice to the EAG was that this would not be expected to have a large impact.
- There were some differences in patient characteristics between CM142 and CheckMate 8HW. The company explored the impact of these via a matching analysis (in Appendix O); this indicated little impact from observed differences (Figure 12, CS Appendix O). The matched data was not used in the main analysis due to reduction in sample size from the matching process (ESS for CM142 reduces to [redacted]), which rendered this analysis unreliable and indicated that there may be a lack of good overlap in patient characteristics between the two studies. Key differences identified between the two studies include more patients in CM142 being from the US/Europe in CM142 Cohort 3 than CM8HW, CM142 not including participants with ECOG 2 and the proportion of participants with Lynch syndrome being moderately higher in CM142. The expected impact of these differences was minimal.

Additionally, there are complexities to use of PPS data when a trial is not yet fully mature as outcomes of early progressors in terms of subsequent therapy may differ to later progressors. The EAG, again, did not consider this a major issue as the CM142 Cohorts contained patients with follow-up of up to 8 years and few PFS events were observed at 5 years indicating.

PPS was defined as time from progression to death. The median time to death after experiencing a progression event was [redacted] months (95% CI: [redacted]). The company selected a log-logistic model fit on the basis that this had the best AIC of the curves considered to be both clinically plausible and to have a good statistical fit (log-logistic, Weibull and gamma). The EAG noted that the Weibull and gamma provided lower estimates of landmark survival at later timepoints ([redacted] at 10 years and [redacted] at 20 years vs [redacted] and [redacted] for the log-logistic).

The EAG's clinical expert considered all of the curves presented for PPS equally plausible and noted that sometimes patients who have had immunotherapy get more slowly growing disease afterwards compared to patients who have never had an IO (based on anecdotal evidence). They did not consider, however, that outcomes for 2nd line chemotherapy would be expected to be better than 2nd line NIVO + IPI, even given this effect.

In their base case, the company did not use data from CM142 Cohort 2 (2L+ NIVO + IPI) to investigate the impact of using NIVO + IPI as a subsequent treatment (n=119) although this would appear the most relevant data to use post chemotherapy. This was justified by citing TA709, where equality of subsequent treatments was assumed. At the time NIVO + IPI was not available as a subsequent treatment and therefore this justification does not apply. The company provided this data as a scenario analysis in response to clarification question B21.

The company noted in Appendix O that "it is expected that around 80% of patients in CM-8HW have crossed over from chemotherapy to Niv + Ipi". Given that the company have submitted evidence assuming a benefit of [redacted] undiscounted life years for NIVO + IPI over chemotherapy in their previous TA for previously treated patients (TA716; provided in CQ Table 46) it would appear very surprising that they now consider treatment with NIVO + IPI to have no benefit at all in this setting. They also note: "the assumption of equal post-progression survival may not be appropriate with regards to Niv + Ipi versus chemotherapy, for because patients who receive IO therapies at 1L are unlikely to receive them at 2L after progression, whereas patients who receive chemotherapy at 1L can receive IOs at 2L, as they have not progressed while on IOs previously. As more efficacious treatment options may be available to 1L chemotherapy patients instead of 1L IO patients based on the above, it could be reasoned that post-progression survival may differ between the two treatment arms and that carrying out the survival analyses in this manner could result in pessimistic outcomes for the chemotherapy arm." They note that clinicians at the advisory board conducted by the company did not agree with this assumption either. The EAG agree with this logic and consider this assumption not to be valid.

Some data was presented for the impact of cross-over to PEMBRO in the KN-177 trial which the company state warrants assuming equal effectiveness as PPS for SOC with a 100% predicted switch to PEMBRO being similar to PPS post PEMBRO (Figure 9 Appendix O). The EAG did not agree that this assumption is translatable to the impact of NIVO + IPI (as this submission argues that NIVO + IPI is more effective than PEMBRO) and note that in TA709 subsequent use of pembrolizumab is not allowed and both arms assume a mix of standard chemotherapy treatments is used making the assumption of equal PPS more plausible.

Company scenario analysis – use of NIVO + IPI data for PPS post chemotherapy

The scenario analysis presented using data from CM142 Cohort 2 (2L+ NIVO + IPI) to inform PPS after chemotherapy assumes an exponential fit. No justification was provided for this and the EAG considered this unlikely to be appropriate. The EAG did not have the data available to perform alternative curve fits ourselves. Additionally, BSC costs were removed from both arms as: “patients in the chemotherapy arm would be living for a long period in the progressed disease state, BSC costs were no longer appropriate to apply for the entirety of that time.” The need to do this indicates that there may be a more fundamental issue with how BSC costs are applied in this model which is explored further in Section 4.2.8.3.

The company assumed that PPS will be similar for patients receiving either NIVO + IPI or PEMBRO after chemotherapy due to time limitations in responding to clarification questions. The EAG tested the impact of this in exploratory scenario analysis.

4.2.6.5. Validity of predicted OS

Absolute survival

The company provided validation of predicted OS using data from KN-177 and pooled data from CheckMate 142 (unclear which cohorts) in response to clarification questions (Figures 28 and 29). Validation versus KN-177 indicates that both modelled arms lie initially above the KN-177 curves and then later on lower with the same pattern. Whilst the chemotherapy arm of KN-177 has initially better PFS than observed in CM8HW fewer subsequent treatment options were available to patients in KN-177; the pattern observed in the validation therefore reflects the opposite of what would be expected. Equally, it may indicate underprediction of outcomes for PEMBRO relative to NIVO + IPI.

Validation versus CheckMate 142 demonstrated that the model consistently overpredicts compared to the observed data. The EAG would have preferred to see a comparison with the relevant cohorts from CheckMate 142 (Cohort 1 for NIVO and Cohort 3 for NIVO + IPI).

Within the model around 60% of patients are predicted to be long-term survivors (% remaining alive at 10 years) on the NIVO + IPI arm. This compares to a BICR-assessed CR rate of only [redacted] and ORR of [redacted] [Table 63 CQ response; CM142 data as CM8HW data are not available] again indicating that predictions may be optimistic. Clinical expert advice to the EAG was that whilst RECIST criteria can have issues for IO treatments as sometimes there is residual mass left with no cancer in it, they would not expect a long-term survival rate this high given the ORR.

Figure 16: Comparison of modelled OS with observed pooled data in CheckMate 142

Abbreviation: IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; SOC, standard of care
Source: Figure 29 Clarification Response

The EAG considered the curve fits presented for NIVO + IPI relative to PEMBRO to be essentially unvalidated. The company failed to provide data for OS from CM8HW in response to

clarification questions and the validation that has been provided using CM142 data shows over-prediction. The EAG considered the lack of provision of OS data to be unjustified as death data is available to the company as deaths are also a safety endpoint (see Table 8.3-1 of the CSR for instance). The EAG noted that there were 44 deaths on the NIVO + IPI arm (22%) and 37 deaths on the chemotherapy arm (42%); whilst these data are immature there is enough information available to be able to provide some validation. The initial datacut of KN-177 had 56 deaths in the PEMBRO arm (37%) versus 69 in the chemotherapy arm (45%)[34] indicating that there may be some advantage in OS for NIVO + IPI. However, without KM data this information was difficult to interpret. Given that no data was provided to allow validation of the OS fits for NIVO + IPI the EAG tested scenarios including equal effectiveness to PEMBRO which the EAG considered to be a plausible, if conservative, scenario as it is common for gains in PFS not to translate to gains in OS in oncology.[21]

Implications for treatment effect

Figure 17 shows that the implied treatment effect on OS increases against both CHEMO and PEMBRO over the first 35 years of the modelled time horizon.

Figure 17: Modelled treatment effect on OS

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; OS, overall survival
Source: EAG plot based upon data in the Patient Distribution sheet in the model

4.2.6.6. Time on treatment

The company stated in Doc B that they used Kaplan Meier data from the CM8HW trial to model TTD for NIVO + IPI and chemotherapy. As [redacted] and [redacted] patients remained at risk respectively for NIVO + IPI and chemotherapy at the end of follow-up the EAG considered this appropriate. On investigation of the model, however, the EAG found that time on treatment had in fact been set equal to PFS in the model and KM data had been deleted from the model supplied. The EAG does not recommend this as it does not allow for treatment beyond progression (which was allowed in CM8HW and KN-177 and the draft SmPC does not specifically mention stopping on progression for CRC). The EAG received 54 amended model files containing the KM data from the company 27th August 2024; one for the base case and one for each scenario analysis. The EAG considered the revised analysis including TTD to be more appropriate.

For NIVO + IPI and PEMBRO a stopping rule applies, resulting in a maximum treatment duration of two years. However, it is possible for patients to have a treatment duration slightly over two years. This can happen where there is a dose interruption during time on treatment. This is reflected in the Kaplan Meier data included in the economic model.

For PEMBRO as Kaplan Meier data for TTD was not available the company assume that the duration of treatment is equal to NIVO + IPI. The EAG did not agree with this assumption as although a naïve comparison of the mean duration of treatment for NIVO + IPI and PEMBRO indicates similar outcomes [redacted] vs 13.3 months the chemotherapy arm has a longer duration of treatment in KN-177 than in CM8HW (8.3 vs [redacted] months). This makes a naïve comparison biased in favour of NIVO + IPI as the treatment duration with PEMBRO relative to NIVO + IPI will be overestimated.

At clarification (CQ B12), a scenario analysis was requested to explore this, the company did not provide this as they argued that the way TTD was accounted for differs between trials (patients still on treatment are censored in CM8HW whereas they are not censored in KN177). This is not the case as the data present is mean duration of treatment data using the same definition (i.e. not censoring per the TTD endpoint). The company also argue that earlier than expected discontinuation of chemotherapy is due to crossover to receive immunotherapy (CM8HW is an open-label trial) which was not as possible during KN-177 meaning that the difference in duration of chemotherapy treatment is unlikely to impact on the face validity of assuming equivalent time to treatment discontinuation between NIVO + IPI and pembrolizumab. This argument does not hold face validity as crossover to PEMBRO was possible in KN-177. The EAG therefore explore the impact of alternative assumptions for TTD: in particular applying the HR used for TTP to the TTD Kaplan Meier curve.

4.2.6.7. Adverse events

AEs were included in the model based upon naïve inputs from CM8HW for NIVO + IPI and chemotherapy and KN-177 for PEMBRO. This is not ideal as it does not take into account differences in the chemotherapy rates between trials but is not considered likely to cause a major issue as AEs have limited impact within the economic analysis (difference between treatments of [redacted]) due to low event numbers and AE disutilities not being applied in the base case to avoid double counting with treatment-specific utilities. The criteria used to include AEs were sufficiently inclusive:

- AEs of special interest to immunotherapies
- AEs grade ≥3 with an incidence of ≥5%

4.2.7. Health-related quality of life

4.2.7.1. Impact of health state and treatment received

Utilities for the modelled health-states were taken from the CM8HW trial. CM8HW included the EQ-5D-3L using the UK tariff with assessment at a minimum frequency of once every 8 weeks whilst patients were on treatment and 3 monthly during survival follow-up visits.

The majority of observations were for patients who were progression-free with a limited number of observations available in progressive disease particularly for patients on the chemotherapy arm (Table 21). Completion rates were high on the NIVO + IPI arm during the treated period but were considerably lower during safety and survival follow-up ([redacted] of the expected population; CS Table 68). Completion rates were consistently lower in the chemotherapy arm including at baseline ([redacted] lower at most timepoints).

Table 21: **CM8HW EQ-5D-3L observations**

	NIVO + IPI (N=202)		Chemotherapy (N=101)		Overall (N=303)	
	N	Obs.	N	Obs.	N	Obs.
Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression						
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PD, progressed disease; PF, progression-free

Source: replicated from CS Table 67

A mixed model approach was used for estimation of mean utility values in each health state with health state and treatment and their interaction included as a fixed effect and a random intercept was used to account for repeated measurements within each participant.

Utility scores in the progression-free state ([redacted]) were similar to those in the progressed disease state ([redacted]); this is likely due to lower completion rates for timepoints post progression with sicker patients not completing questionnaires and also limited follow-up being available post-progression due to the immaturity of the trial data. In fact, in the NIVO + IPI arm PD utilities

were higher than those in PF indicating a lack of face validity to the estimates. Studies identified in the SLR indicated that utilities fall as the line of treatment increases with utilities of 0.59 being applied to last-line disease in TA866.[35]

Differences were observed across arms in both the PF and PD states ([redacted] In both cases utilities were higher for NIVO + IPI than for chemotherapy. In PF the EAG considers the difference reasonable as NIVO + IPI has a more favourable safety profile and is administered less frequently than its chemotherapy comparator. In PD this would appear counter-intuitive as TA716 incorporated higher utilities for patients receiving NIVO + IPI in the previously treated setting than patients receiving chemotherapy.[36] Although the utilities used in TA716 are redacted in the submission the EAG note that the company state in their submission that the utility values observed were higher than in other published literature and comparable to a general population utility value of 0.842 (CS for TA716; page 112).

There are also issues of inconsistency in the definition of PFS applied with how subsequent lines of treatment are modelled which were explored in the company's response to clarification questions (CQ B14). When the company provided an analysis where patients who switched treatment were removed from the PF utility value; this resulted in a higher utility for both arms ([redacted]). These results are difficult to interpret as simply removing patients is not appropriate, but they do demonstrate some sensitivity in the utility values to PFS definition. Unfortunately, the company did not provide the requested analysis, which was to re-run the utility analysis for both PF and PD reclassifying receipt of subsequent treatment as a progression event.

For PEMBRO, it was assumed that PEMBRO utility values would be equal to NIVO + IPI based on a comparison of NIVO + IPI and NIVO from the previously treated cohorts of CM142 which showed a non-significant trend for improved HRQoL for NIVO + IPI versus NIVO monotherapy.[37] The observed difference in utility in the progression-free state using data from KN-177 indicates a utility difference of 0.056 which would appear broadly in line with the data for NIVO + IPI and therefore the EAG would consider this assumption reasonable despite there being some issues with using NIVO data as a proxy for HRQoL with PEMBRO as is given less frequently than NIVO.

4.2.7.2. Impact of adverse events

AE decrements were only applied in the model in scenario analysis (which contrasts what is written in Doc B). The EAG assumed this is to avoid double counting with treatment-specific utilities being used in the base case. The AE decrements and the duration they are applied for in the company model appear broadly reasonable (1 week for the majority of AEs; 108 days for endocrine AEs; see CS Table 70 for decrements). The EAG tested the impact of including AE decrements on top of treatment specific utilities in scenario analysis (as treatment specific utilities may underestimate the impact of AEs due to lack of completion of questionnaires during serious AEs).

4.2.7.3. Age adjustment

Age adjustment of utilities to account for the impact of aging over time was appropriately included in the model using age- and sex- adjusted utilities using the UK index of health state utility decline from Ara et al.[38,39] There are some minor issues with how this is implemented in that the lifetables used do not align with guidance to continue to use 2017-2019 lifetables due to the impact of COVID on the current version and the model does not account for the changing sex mix of the population due to differential mortality in males and females.[40] These issues are only expected to have a minor impact.

4.2.8. Resources and costs

4.2.8.1. Drug and administration costs

Table 21 provides the drug costs associated with each of the available treatments. NIVO + IPI is given more frequently than PEMBRO (the vast majority of patients receive this Q6W; assumed 100% in the company base case). All 3 IOs are available with commercial access arrangements as are cetuximab and panitumumab. A 2-year stopping rule applies to both PEMBRO and NIVO as part of NIVO + IPI. This stopping rule was included in the CM8HW trial, however, there is uncertainty about how this would be applied in practice (see Section 3.2.2.3). The EAG note that the company's assumptions in this appraisal that the trial protocol will be followed may be optimistic and present a scenario analysis assuming that patients receive treatment for longer in line with CM142 where a 2-year stopping rule was not applied.

All chemotherapy treatments are given Q2W and, except for cetuximab and panitumumab, are available as generics. It is assumed that all patients receive 100% of their expected dose per the SmPC.

The company in their base case costed chemotherapy according to advisory board opinion on the proportion of patients who would receive each type of treatment in practice (CS Table 82). The EAG did not agree with this approach as this divorces costs and effectiveness. Whilst this may be reasonable for non-targeted treatments this is less reasonable for combinations including cetuximab and panitumumab. The EAG therefore requested the company to provide an analysis using trial data. The company provided an analysis using reweighted data primarily from CM8HW, excluding bevacizumab as this is not available in UK clinical practice. This adjusted split increased the cost of chemotherapy from [redacted] Q2W in the base case to [redacted] due to the increased use of cetuximab-based regimens. The EAG therefore considered uncertainty around the impact of the type of chemotherapy regimen to be resolved.

The EAG identified coding errors in the drug costing sheet in the application of method of moments for chemotherapy and in the response to B18 in the application of wastage for ipilimumab (see Section 6.1); these have been corrected in Table 22.

Table 22: Dosing schedule and list price cost per cycle

Drug	Administration frequency	Dose per cycle	Treatment costs per cycle
			Adults
NIVO	240mg Q3W x 4 cycles	240mg	£2,633
IPI	1mg/kg Q3W x 4 cycles	Mean dose 70.5mg Using HSE*	£7,500 £7,920
NIVO	480 mg Q4W after 4 cycles up to 2 years	480mg	£5,266
PEMBRO	400mg Q6W up to 2 years	400.00 mg	£10,520
FOLFOX	Q2W: Fluorouracil bolus 400mg//m^2 and infusion 2,400/m^2 Leucovorin 400mg/m^2 Oxaliplatin 85mg/m^2	-	£59.02
FOLFIRI	Q2W: Fluorouracil bolus 400mg//m^2 and infusion 2,400/m^2 Leucovorin 400mg/m^2 Irinotecan 180mg/m^2	-	£88.10
CAPOX	Q2W: Capecitabine 1,000 mg/m^2 Oxaliplatin 85mg/m^2	-	£35.35
FOLFOXIRI	Q2W: Fluorouracil infusion 3,200mg/m^2 Leucovorin 350mg/m^2 Irinotecan 165mg/m^2 Oxaliplatin 85mg/m^2	-	£101.96
FOLFOX + cetuximab	Q2W: Fluorouracil bolus 400mg//m^2 and infusion 2,400/m^2 Leucovorin 400mg/m^2 Oxaliplatin 85mg/m^2	-	£1,733.16

Drug	Administration frequency	Dose per cycle	Treatment costs per cycle
			Adults
	Cetuximab 500mg/m^2		
FOLFIRI + cetuximab	Q2W: Fluorouracil bolus 400mg//m^2 and infusion 2,400/m^2 Leucovorin 400mg/m^2 Irinotecan 180mg/m^2 Cetuximab 500mg/m^2	-	£1,762.24
FOLFOX + panitumumab	Q2W: Fluorouracil bolus 400mg//m^2 and infusion 2,400/m^2 Leucovorin 400mg/m^2 Oxaliplatin 85mg/m^2 Panitumumab 6mg/kg	-	£1,955.47 / £2,080.91 using HSE*
FOLFIRI + panitumumab	Q2W: Fluorouracil bolus 400mg//m^2 and infusion 2,400/m^2 Leucovorin 400mg/m^2 Irinotecan 180mg/m^2 Panitumumab 6mg/kg	-	£1,984.55 / £2,109.99 using HSE*

Abbreviations: FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, folinic acid, 5-fluorouracil, oxaliplatin and irinotecan; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab.

Note: * Health Survey England data were used to account for the distribution of expected patient weights in CQ B18

Unit costs for drug administration were based on National schedule of NHS costs 2021–2022.[25] Chemotherapy doublet and triplet regimens were assumed to require complex IV infusion. PEMBRO and NIVO + IPI were both assumed to be simple IV administrations. We note that this was not in line with TA716 where NIVO + IPI was assumed to require a complex chemotherapy administration. However, as the company applied separate administration costs for NIVO and IPI during the first 4 treatment cycles the EAG considers that the resulting cost is similar to what would have been expected.

4.2.8.2. Subsequent treatment costs

Type of subsequent treatment

In the model the company base case assumed that 54% of patients across all arms will receive a subsequent treatment (per TA709 assumption for PEMBRO). This contradicts the company's written statement that this is not realistic in CS Section B.3.5.1.4 and does not align with trial evidence. Of those patients who received subsequent treatment the company base case assumed that all patients treated with PEMBRO and NIVO + IPI received treatment with the lowest cost chemotherapy (FOLFOX) on progression and that all patients received NIVO + IPI after progression on chemotherapy. Again, this divorces costs and effectiveness as the transition probabilities used to model PPS for all arms are from CM142 where patients would not receive NIVO + IPI again and therefore are likely to underestimate the effectiveness of NIVO + IPI following chemotherapy.

The EAG therefore requested data on subsequent treatments received in CM8HW and CM142 to inform the proportion of progressors fit enough for treatment, the types of chemotherapy regimens used, and their duration of treatment. While some information was received on the types of subsequent systemic therapies the sample size was small (n=[redacted] from Cohort 3 in CM142; n=[redacted] for NIVO + IPI in CM8HW and n=[redacted] for chemotherapy).

Table 23 shows firstly that not all patients receive a subsequent systemic therapy after progression [redacted] In clinical practice immune-oncology treatments cannot be used in first and second-line due to a lack of data for the effectiveness of retreatment.

Table 23: Comparison of subsequent treatments received within trials and in the model

	CM8HW		**CM142 Cohort 3**	**KN-177 from TA709**		**Base case assumption**		**Scenario assumption**	
Subsequent therapy type	NIVO + IPI	Chemo	NIVO + IPI	PEMBRO	Chemo	NIVO + IPI & PEMBRO	Chemo	NIVO + IPI & PEMBRO	Chemo
Any systemic therapy / number of PFS events + number censored for subsequent treatment	[redacted]	[redacted]	[redacted]	54.7%	83.2%	100%	100%	100%	100%
Anti-PD-1 or anti-PD-L1	[redacted]	[redacted]	[redacted]	0%	0% (not available at the time)		100%		[redacted] NIVO + IPI [redacted] PEMBRO
EGFR inhibitors	[redacted]	[redacted]	[redacted]	5%	0%				
VEGFR targeted therapy	[redacted]	[redacted]	[redacted]	51%	82%				
Other systemic therapies (standard chemotherapies)	[redacted]	[redacted]	[redacted]	43%	18%	100% FOLFOX		56.9% FOLFOX 43.1% FOLFIRI	[redacted] FOLFOX [redacted] FOLFIRI

	CM8HW		CM142 Cohort 3	KN-177 from TA709		Base case assumption		Scenario assumption	
MEK, NRAS and BRAF inhibitor	[redacted]	[redacted]	[redacted]	0%	0%				

Abbreviations: CM, CheckMate; EGFR, epidermal growth factor receptor; IPI, ipilimumab; KN, KEYNOTE; NIVO, nivolumab; PEMBRO, pembrolizumab;

Notes:

proportions shown for CM8HW and CM142 are out of the number of patients receiving any systemic therapy, they may add up to more than 100% as patients can receive more than on treatment.

* including other chemotherapy and unassigned chemotherapy

Source: CQ Table 30, Table 33 -Table 35, CS Section B.3.5.14

Given that the available trial data for subsequent treatment post chemotherapy either came from an era prior to reimbursement of NIVO + IPI or included crossover within the protocol the EAG sought additional data on what would be expected in practice. The EAG first consulted a clinical expert who noted that a reasonably high proportion of patients are not fit enough to receive NIVO + IPI in the second-line setting (around 50%) and therefore receive PEMBRO. The EAG then requested data from Peter Clark, the CDF lead, on the number of patients receiving NIVO + IPI and PEMBRO at second and subsequent lines. He stated that there are around 35 patients per year receiving NIVO + IPI and around 25 patients per year receiving PEMBRO.

The EAG provided insights from the clinical consultation to the company within clarification questions and requested a scenario analysis using trial data to determine the split of subsequent treatments received. The company provided a scenario using data from KEYNOTE-177 (NIVO + IPI and PEMBRO arms) and CM8HW (chemotherapy arm). Both sets of data were reweighted to exclude bevacizumab and cetuximab. While cetuximab is used in the second line setting in the UK according to clinical expert advice received by the EAG, it was excluded by the company because the combination of cetuximab and encorafenib (TA668) was not used in CM8HW. This is not a valid reason to exclude this combination and highlights an area of lack of generalisability of the trial data to the NICE decision problem.

These subsequent treatment distributions were applied in two scenarios: one applied post-progression survival in the chemotherapy arm aligned with submission base case analysis, while the other used post-progression survival from CM142 Cohort 2 (2L+ NIVO + IPI) for PPS on the chemotherapy arm.

Finally, the EAG noted that encorafenib + cetuximab was noted as a subsequent treatment option for BRAF mutant patients in the CS and by clinical advice to the EAG. This is not included in the company model and has the potential to be used by a reasonable proportion of patients (>25%). The EAG conducted scenario analysis to determine whether use of this treatment as an alternative for all BRAF mutant patients would impact on cost-effectiveness. Cetuximab is only used with encorafenib as a subsequent treatment as cetuximab with either FOLFOX or FOLFIRI is only funded at first-line.

Duration of subsequent treatment

The company assumed a 2-year stopping rule for NIVO + IPI and PEMBRO in line with TA716. The company, however, assumed that all patients receive exactly 2 years of treatment, which

would appear highly unrealistic and not in line with the assumptions in this submission or in TA716. The company assumed a mean duration of treatment of 20 weeks for chemotherapy; the source of this was unclear but it would appear reasonable given the mean duration of treatment for chemotherapy is [redacted] weeks in CM8HW (CSR Table 6.1-1). The EAG requested data from CM8HW and CM142 on the duration of subsequent treatment, however, this was not collected.

Peter Clark was asked to provide any data available on treatment durations for NIVO + IPI and PEMBRO. In both cases he noted that the treatment duration is open for responding patients. The EAG have since checked the Blueteq forms and whilst there is a stopping rule written in for PEMBRO there is not for NIVO + IPI for previously treated patients. The Blueteq forms advise that patients can continue if the patient and clinician agree. The clinical expert advisor to the EAG noted that this came up recently in a clinical forum and that there was a mixture of answers as to whether treatment should stop at 2 years as clinicians have to juggle the lack of evidence for an improvement in outcomes with longer treatment and uncertainty about when to stop if not at 2 years with patient anxiety about coming off treatment and there not being an option to reinitiate treatment if patients lose response. The EAG did not have access to data on the duration of treatment for Cohort 2 in CM142 and were therefore unclear on what the mean duration of treatment for previously treated patients might be expected to be. In the absence of such data the EAG assumed in its base case that it might be similar to what was observed at first-line. The EAG also noted that this highlights the importance of the stopping rule for first-line treatment being written either into the SmPC or the Blueteq form.

Application of costs

The EAG had major concerns about the method used to apply subsequent treatment costs which rather than apply on entry into the progressive disease state (more common) applies a cost for all cycles in PD. The equation used in the model is presented in Equation 1. Based on the economic model, for all treatments the mean cycles spent in progression ([redacted]) is taken from RMST analysis of CM142 NIVO + IPI data (unclear which cohorts). The effect of the calculation below is to produce a mean per cycle cost for each subsequent treatment which is then applied to the number of cycles spent in progressive disease in the model. This is fundamentally flawed as if the mean cycles spent in progression is different in the model to CM142 (which it is) the stopping rule for NIVO + IPI in 2nd line cannot be properly handled. The EAG corrections therefore instead applied the cost of a course of treatment on entry into progressive disease.

Equation 1: Calculation of subsequent treatment costs

$$Cost\ of\ subs\ trt\ per\ cycle = \%\ in\ PD * \%\ getting\ a\ subs\ trt * \sum_{i=1}^{n=n\ subs\ trt\ options} \%\ receiving\ trt\ type_i * \frac{cost\ of\ a\ course_i}{mean\ cycles\ in\ progression: CM142}$$

4.2.8.3. Health state costs

The company stated that resource use estimates for the progression-free and progressed disease states were derived from those applied during TA709. These costs would appear high when compared to many other oncology submissions in particular:

- Visits with a consultant are assumed to occur once every 2 weeks on top of drug administration for the entire patients lifetime whilst progression free
- The BSC cost from Färkkilä (2015)[41] is assumed to apply to the entire time spent post-progression. In that paper the mean duration of palliative care was 181 days which is considerably shorter than the time spent in post-progression in any of the arms in this model

The EAG compared costs across prior submissions (Table 24) and found these to be highly inconsistent. This includes even the direction of the difference (in some TAs the post progression state is cheaper than the pre progression state). The use of Färkkilä (2015)[41] dates back to the TA439 MTA, at which time it was applied only to patients at 3rd line indicating as per the above at this represents costs for patients who have exhausted all other options. The EAG considered applying this to patients from 2nd line onwards as in this submission is inappropriate.

Given this the EAG sought clinical expert input to inform resource use. Clinical expert advice to the EAG was that, for IOs, clinical consultation is scheduled to align with infusions. Once patients have finished active treatment with an IO they are then initially seen and scanned every 3 months for 1 – 2 years, then once every 6 months, and are then discharged if they remain progression free at 5 years. For chemotherapy, clinical advice to the EAG was that patients would be seen before each cycle of chemotherapy (every 2, 3 or 4 weeks depending on the type) and that once active treatment stopped the same rules would be observed as for IOs. These schedules apply to active treatment at any line of therapy.

Clinical expert advice to the EAG was that patients are not usually referred to palliative care until the last few weeks of life as there have been considerable cuts to palliative care services. In some cases, patients may be able to access such services earlier (e.g. via an enhanced board of care service) for symptom control difficulties or discussions about treatment options if they are unsure whether to continue. They stated that approximately a third of patients are referred for these services and that the majority are referred for the last few weeks of life.

Table 24: Comparison of health state costs across TAs

Source	Pre-progression cost per month	Post-progression cost per month
Current model	£579	£1,623
TA866	£250 (on treatment)	£185
TA716	£11.67	£203
TA709	£533	£1,600
TA668	£218 (non-FOLFIRI), £402 (FOLFIRI)	£182
TA439	Not reported but assumes 2 oncologist visits per week; applies to both 1st and 2nd line	£1,254 – but this is only applied for 3rd line
TA405	£203 (on treatment) £182 (BSC)	£193

Abbreviations: BSC, best supportive care; FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; TA, technology appraisal

Source: Appendix I, model cells 'Input conversion'!K63:L68 and calculations from TAs missing from Appendix I taken from manufacturer submissions except for TA439 which uses the independent assessment group model

4.2.8.4. Adverse event costs

Unit costs per AE were based on prior TAs, the literature and National schedule of NHS costs. This appeared reasonable.

4.2.9. Uncertainty

The methods used by the company to incorporate uncertainty via probabilistic analysis appear broadly reasonable with the following exceptions:

- The proportion of patients receiving each chemotherapy regimen was not included
- The proportion of patients receiving subsequent treatment was not included and the standard error was assuming 20% of the mean when trial data is available

- The cost per administration of mono and combo IO therapy was included even though drug costs are fixed
- Time on treatment for mono and combo IO therapy as subsequent treatment was assuming a SE of 20% of the mean even though a stopping rule exists
- Adverse events incidences were assuming a variation of 20% of the mean even though data exists from the relevant trials
- No uncertainty is included around the TTD KM

Patient characteristics are not included in the PSA in the model which the EAG agreed with as the purpose is to model outcomes for a fixed decision problem population and in any case the true impact of variation is not incorporated as none of the characteristics are included in the parametric models fitted for effectiveness. The EAG also noted that the multivariate normal (not normal) distribution is used for survival parameters as would be expected and that the ITC samples from the NMA CODA as would be expected.

The company also present one-way sensitivity analysis for model parameters in the form of tornado diagrams and a wide variety of scenario analyses:

- Varying model time horizon (5 years reflecting the extent of data for NIVO + IPI in CM142)
- CM142 PrePS data applied in addition to general population mortality
- Use of alternative ITCs
- Use of alternative curve fits for TTP including use of spline models for TTP (response to CQ B7)
- Comparison to panitumumab + FOLFOX using data from the ITC including PRIME
- Assuming patients receive chemotherapy after chemotherapy (rather than NIVO + IPI)
- Basing subsequent treatment receipt on CM8HW and KN177 (response to CQ B19)
- Using utilities from TA709 and TA439
- Utilities removing patients who switched treatment prior to progression (response to CQ B14)

- Varying the cost of the chemotherapy comparator to the lowest and highest cost regimens
- Use of trial-based chemotherapy split (response to CQ B16)
- Inclusion of drug wastage using data from HSE for patient weights (response to CQ B18)

4.2.10. Subgroups

4.2.10.1. dMMR/MSI-H status

Subgroup analysis was provided for patients with centrally confirmed dMMR/MSI-H status. Only NIVO + IPI and chemotherapy inputs were changed and therefore this scenario should be interpreted with caution

4.2.10.2. Mutation status

In response to clarification question B20 the company provided scenario analysis looking at the impact of mutation status on cost-effectiveness based upon the type of chemotherapy that would be received. They assume no change in efficacy as in the CM8HW subgroup analysis, the HR for progression in the KRAS-mutant subgroup was similar to the HR for the whole population 0.24 [0.09, 0.63] vs. 0.20 [0.14, 0.31] in the centrally confirmed population. This argumentation misses the point that baseline risk may vary by mutation status and therefore results are likely to be highly flawed. In the chemotherapy arm, median PFS was 5.9 months, 9.2 months and 5.7 months for the total centrally confirmed population, the BRAF mutation subgroup and the KRAS/NRAS mutation subgroup, respectively. No data was presented for patients without either mutation to allow full comparison.

The analysis assumes presents 8 scenarios for the costs of chemotherapy: 100% FOLFOXIRI for the RAS mutation subgroup, 100% cetuximab with FOLFOX or FOLFIRI for EGFR expressing RAS wild type mutation, 100% panitumumab with FOLFOX or FOLFIRI for RAS wild type EGFR expressing and non-EGFR expressing mutations, 100% MFOLFOX6, FOLFIRI or CAPOX for patients with no mutation. The scenario analysis had limited impact on cost-effectiveness.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The results presented in this report incorporate a PAS discount for the NIVO and IPI and list prices for all comparator treatments and are taking from the addendum supplied to the EAG 27th August 2024. This report is accompanied by a confidential appendix that reports the results of analyses when confidential prices for comparator treatments are included.

5.1.1. Base case results

The results reported by the company are shown in Table 25. The company do not report fully incremental analysis instead reporting comparisons to each treatment individually. The company provide comparison to chemotherapy as a blended comparator and also to each type of chemotherapy in scenario analysis assuming equal effectiveness (Table 15, addendum). The ICER in comparison to FOLFOX in this scenario is £2,361.

The deterministic and probabilistic results are reasonably consistent although the cost of the blended chemotherapy comparator in the initial PSA supplied the company was unexpectedly higher than in the deterministic analysis (potentially due to the error identified in the PSA sampling of chemotherapy type; see Section 6.1). PSA was run separately for each comparator without applying a pre-set random number seed, leading to slight variations between runs even with identical model inputs; this is not ideal nor required as instead PSA could be run once with all comparators included. However, the EAG did not consider this has led to major issues in interpreting the results.

The new PSA supplied by the company in their addendum is reported in Table 2. The EAG noted, however, that this does not match the PSA supplied in the Excel file at the same time and that the discounted costs for NIVO + IPI in Table 3 supplied by the company were incorrect and have therefore been labelled as such (as the incremental presented cannot be matched to these and the cost for NIVO + IPI matched the deterministic base case).

Table 25: Company base case results, adults (including PAS for NIVO and IPI)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£1,836
Company probabilistic base case vs PEMBRO					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Company probabilistic base case vs chemotherapy					
NIVO + IPI	Error in company table	[redacted]	[redacted]	[redacted]	
Chemotherapy		[redacted]	[redacted]	[redacted]	£891

Abbreviations: ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALYs, quality-adjusted life years

5.2. Company's sensitivity analyses

5.2.1. Deterministic sensitivity analyses

Figure 18 and Figure 19 demonstrated that the model was most sensitive to the cost and frequency of outpatient appointments in the comparison to pembrolizumab as these continue throughout the whole of the PFS period which is the main difference between the treatments and best supportive care costs which continue throughout the whole of the PPS period which differs between the treatments due to increased TTP for NIVO + IPI vs PEMBRO. In the comparison versus chemotherapy the model was most sensitive to parameters linked with the cost of subsequent NIVO + IPI treatment followed by the same parameters observed in the comparison to PEMBRO.

Survival parameters are not included in OWSA which limits the usefulness of these plots in informing decision-making although the EAG agreed that including correlated parameters in OWSA is not appropriate.

Figure 18: OWSA outcomes: NIVO + IPI versus PEMBRO (including PAS for NIVO and IPI)

Abbreviations: CT, computed tomography; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; OWSA, one-way sensitivity analysis; PAS, patient access scheme; PEMBRO or Pem, pembrolizumab; MRI, magnetic resonance imaging

Figure 19: OWSA outcomes: NIVO + IPI versus chemotherapy (including PAS for NIVO and IPI)

Abbreviations: ICER, incremental cost-effectiveness ratio; IO, immunotherapy; IV, intravenous; IPI, ipilimumab; MRI, magnetic resonance imaging; NIVO, nivolumab; OWSA, one-way sensitivity analysis; PAS, patient access scheme; CT, computed tomography; MRI, magnetic resonance imaging

5.2.2. Probabilistic sensitivity analysis

Figure 20 and Abbreviations: ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; QALY, quality adjusted life-years

Figure 21 show that the profile of uncertainty differs in the comparison to PEMBRO and chemotherapy with a tighter spread of samples in the within-trial comparison to chemotherapy as would be expected. A small minority of samples in the comparison to PEMBRO generate negative QALYs.

Figure 20: ICER scatterplot: NIVO + IPI vs PEMBRO (including PAS for NIVO and IPI)

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; QALY, quality adjusted life-years

Figure 21: ICER scatterplot: NIVO + IPI vs chemotherapy (including PAS for NIVO and IPI)

Abbreviations: ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; QALY, quality adjusted life-years

5.2.3. Scenario analyses

The scenarios which had the largest impact were:

- Assumptions related to PPS and subsequent treatment
  - Using equal costs for chemotherapy and NIVO + IPI increased the ICER to [redacted] (with chemotherapy at list price)
  - Use of trial-based subsequent treatment which increased the ICER to £[redacted] vs chemotherapy and led to a non-dominant result vs PEMBRO (both of which are costed at list price)
  - Use of an exponential log rate based on OS from CM142 Cohort 2 which reduces the incremental QALYs versus chemotherapy from [redacted] to [redacted]

- Use of the unanchored MAIC and constant HR NMA (reduced the incremental QALYs gained for NIVO + IPI versus PEMBRO by [redacted]
- Use of a shorter time horizon. This scenario showed that much of the benefit versus chemotherapy is accrued beyond 5 years (the limit of trial data) both in incremental QALYs and in build up of costs (particularly BSC costs post-progression).

Table 26: Company scenario analyses (including PAS for NIVO and IPI)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year time horizon					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of CM-142 data for PrePS on top of general population mortality					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anchored MAIC					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unanchored MAIC					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant HR NMA					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – 2-knot odds spline for TTP for both arms					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Alternative curve fits – lognormal for TTP for NIVO + IPI					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – log-logistic for TTP for NIVO + IPI					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – Gompertz for TTP for NIVO + IPI (clinically implausible)					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – Weibull for TTP for NIVO + IPI					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – gamma for TTP for NIVO + IPI					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – exponential for TTP for NIVO + IPI (clinically implausible)					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – lognormal for TTP for chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – log-logistic for TTP for chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – Gompertz for TTP for chemotherapy					

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – Weibull for TTP for chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – gamma for TTP for chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative curve fits – exponential for TTP for chemotherapy					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison with panitumumab + FOLFOX					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Equal costs in PPS (chemotherapy costs in both arms)					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial based subsequent treatment with PPS in chemotherapy per base case					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS in chemotherapy using exponential log rate [redacted]					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial based subsequent treatment with PPS in chemotherapy using exponential log rate [redacted]					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50:50 PEMBRO and NIVO + IPI post chemotherapy and PPS using exponential log rate [redacted]					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA709 utilities					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA439 utilities					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Removal of patients who switched treatment from PF utility value					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of chemotherapy split from CM8HW					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of weight data from Health Survey for England					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALY, quality adjusted life-years; PrePS, PF to death; MAIC, match adjusted indirect comparison; CM, CheckMate; HR, hazard ratios; NMA, network meta-analysis; TTP, time-to-progression; PPS post-progression survival; TA, technology appraisal; PF, progression-free

Notes: * reproduced by the EAG using the Excel file as the information supplied in the clarification questions addendum related to the scenario where PPS used the exponential log rate ([redacted])

5.2.4. Subgroup analysis

5.2.4.1. dMMR/MSI-H status

Table 16 demonstrates that using the centrally confirmed subgroup increases the predicted costs and QALYs for both arms due to a longer predicted TTP. The increase in QALYs is greater on the NIVO + IPI arm and as treatment costs are limited to 2 years this leads to an

improved ICER. Results are not presented for PEMBRO as a fair comparison cannot be made as central confirmation was not conducted in KN-177.

Table 27: Centrally confirmed dMMR/MSI-H (including PAS for NIVO and IPI)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Centrally confirmed dMMR/MSI-H					
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; dMMR, deficient DNA mismatch repair; MSI-H, microsatellite instability high

5.2.4.2. Mutation status

The company results presented by mutation status in response to clarification question B20 only adjust the cost of the chemotherapy comparator with no amendment to either the baseline or relative risks of events and are therefore considered of limited use and not presented by the EAG. Whilst data from CM8HW indicates that the treatment effect for NIVO + IPI is likely to be consistent across subgroups the baseline risk is not. In particular, for the BRAF mutation subgroup where the median PFS is considerably higher than for the total centrally confirmed population (9.2 vs 5.9 months). An improved PFS for standard chemotherapy is likely indicate a lower chance of cost-effectiveness for treatment with NIVO + IPI.

5.3. Model validation and face validity check

The company presented validation versus long-term OS data in KN-177 (Table 28) and concluded that:

- OS outcomes for chemotherapy are initially higher in the economic model than in KN-177 (expected). However, by year five, OS is lower in the economic model than in KN-177
- The reasons for the disparity at 5 years are not entirely clear, as outcomes for KN-177 and CM8HW are aligned by 30 months with the KM for CheckMate 8HW being visually lower between 6 and 30 months

- Survival outcomes for pembrolizumab are broadly aligned between KN-177 and the economic model, although slightly lower by year 5 despite initially being higher

The EAG noted that there was a substantial difference in the gap between KN-177 observed data and the modelled projections for PEMBRO when comparing years 1 and 5 ([redacted] decrease in modelled survival vs [redacted] decrease in observed survival). None of the ITC scenario analysis provided much of a better fit to the observed KN-177 data. The constant HR analysis still had a [redacted] gap in modelled versus observed decrease between years 1 and 5.

Table 28: Comparison of economic model outcomes and KN-177

		1 year OS, %	3-year OS, %	5-year OS, %
Chemotherapy	Base case	[redacted]	[redacted]	[redacted]
	KN-177	74.0	50.3	44.2
Pembrolizumab	Base case (fractional polynomial)	[redacted]	[redacted]	[redacted]
	Anchored MAIC	[redacted]	[redacted]	[redacted]
	Unanchored MAIC	[redacted]	[redacted]	[redacted]
	Constant HR	[redacted]	[redacted]	[redacted]
	KN-177	77.8	61.4	54.8

Abbreviations: HR, hazard ratio; KN, KEYNOTE; MAIC, matching-adjusted indirect comparison; OS, overall survival

The company also presented validation versus CM142 Cohorts 3 (1L NIVO + IPI) and 2 (2L+ NIVO + IPI). The company stated that the "economic model initially predicts OS higher than that observed in clinical trial. However, by year two, survival outcomes from the economic model are broadly aligned with CM142 cohort 3 (1L NIVO + IPI) and Cohort 2 (2L+ NIVO + IPI)." The EAG noted that the model predictions lie numerically above the observed data for both cohorts for all 3 timepoints (Document B Addendum Table 18).

Finally, the company presented validation versus TA709 outcomes (Table 29), concluding that "predicted pre-progression LYs are broadly comparable with values output from TA709. However, progressed disease LYs are impacted by the use of immunotherapies as a subsequent treatment, particularly for chemotherapy."

The EAG noted that whilst the differences in progressed disease life years for chemotherapy are expected they are not expected post PEMBRO and may indicate an overestimation of PPS

for NIVO + IPI as well. The EAG also noted the predicted PFS is higher (by more than 2 life years) in this appraisal for both arms than in TA709 which is not expected as the KM for CM8HW generally lies below that of KN-177; this may indicate the company have selected an overlying optimistic TTP prediction.

Table 29: Comparison of survival outcomes between TA709[42] and current economic model

Comparator	Appraisal	Total LYs	Progression-free LYs	Progressed disease LYs
Pembrolizumab	TA709	6.93	4.56	2.37
	Current	[redacted]	[redacted]	[redacted]
SOC/CAPOX	TA709	3.78	1.21	2.57
	Current	[redacted]	[redacted]	[redacted]

Abbreviations: CAPOX: capecitabine, oxaliplatin; FOLFOX: fluorouracil, folinic acid, oxaliplatin; LY: life year; SOC: standard of care; TA, technology appraisal.

No details of any model quality control or assessment of face vaility were presented.

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified a number of limitations within the company's base case and explored the impact of parameter values, and assumptions, which the EAG believed were more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis.

The scenario analyses presented in Section 6.2 focus on exploring the following issues and uncertainties:

1. Post progression survival
2. Subsequent treatment costs
3. Subsequent treatment type
4. Time to discontinuation for NIVO + IPI and chemotherapy
5. Time to discontinuation for PEMBRO
6. Alternative curve fits for TTP
7. Alternative NMAs
8. Treatment effect waning
9. Alternative health state costs
10. Wastage
11. Chemotherapy split
12. Improved utilities in PPS for chemotherapy
13. Include AE utility decrements
14. Impact on the ICER of additional clinical evidence

In Section **Error! Reference source not found.**, the EAG base-case is presented based on a combination of the exploratory analyses presented in Section 6.2.

6.1. EAG corrections to the company's base case model

In addition to combining the 62 model files received by the EAG into one functioning Excel file, the following calculation errors were found and corrected in the company's base case model:

- The drug formulation sheet for cetuximab 100% had been hard-coded into G390 and 0% into G387 – G389 and G391 – G394 this meant that wastage wasn't accounted for correctly
- In the additional sheet for wastage supplied at clarification questions the male ipilimumab cost column was looking up the female weights
- The Dirichlet distribution was not looking up the correct rows in the Inputs sheet rows 871 – 882
- The centrally confirmed population subgroup analysis broke because the age adjustment didn't include a row for age 60 – the company provided some revisions to correct this which were received by the EAG on the 27th August 2024; the EAG did not consider these as the EAG had already made corrections to the model prior to receipt, this did not impact the base case
- The drug administration cost was linked to PFS rather than time on treatment in the Costs sheet – the company fixed this in the files received on the 27th August
- The number of patients and the proportion female in the ITT population was incorrect in the Main Board sheet – the company fixed this in the files received on the 27th August
- The administration cost for subsequent treatment following NIVO + IPI was incorrect in the Costs sheet – the company fixed this in the files received on the 27th August
- In the model files received on the 27th August the company corrections to age adjustment resulted in the first 2 cycles having an age adjustment value > 1 which was not considered plausible. Given the late receipt of the models the EAG corrected this in the simplest way possible (by setting the value equal to 1 for the first 2 cycles)
- Formulae were amended in the Inputs sheet to use trial data for uncertainty around adverse event rates and subsequent treatment use

The ICER remained similar to the company base case when calculation errors were corrected (Table 30).

Table 30: EAG-corrected company base case deterministic results (list price)

Preferred assumption	Inc costs vs PEMBRO	Inc QALYs vs PEMBRO	Inc costs vs Chemo	Inc QALYs vs Chemo	ICER £/QALY vs PEMBRO	ICER £/QALY vs Chemo	+/- company base case vs PEMBRO	+/- company base case vs Chemo
EAG corrected company deterministic base case								
Fix drug costing errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fix errors in Dirichlet distribution for PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Correct minor error in age adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use trial data for distribution for AEs and subsequent treatments in PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of corrections	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality adjusted life years; PSA, Probabilistic sensitivity analysis; AE, adverse event; Chemo, chemotherapy

Table 31: EAG-corrected company base case probabilistic results (list price)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER £/QALY	Probability of being CE
Comparison to pembrolizumab						
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparison to chemotherapy						
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; Inc, incremental; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio.

6.2. Exploratory and sensitivity analyses undertaken by the EAG

6.2.1. Post progression survival

The EAG explored the following scenarios for PPS:

- PPS for chemotherapy uses the data supplied by the company for clarification response B21a which is an exponential fit to OS for Cohort 2
- PPS for chemotherapy based upon the absolute difference in life years from TA716 ([redacted] vs 1.284 undiscounted life years in the comparison between NIVO + IPI and FOLFOX which implies a HR of [redacted] for NIVO + IPI relative to chemo)
- Reduced PPS for subsequent PEMBRO vs subsequent NIVO + IPI using the company's estimate of the difference at 1st line ([redacted] vs [redacted] life years for NIVO + IPI vs PEMBRO; implied HR for the proportion of patients receiving PEMBRO as a subsequent treatment: [redacted]
- OS for PEMBRO is equal to OS for NIVO + IPI: a multiplier of 53% is applied to the transitions for PPS for PEMBRO to achieve this on top of the EAG base case
- Equal PPS to TA709 for PEMBRO and NIVO + IPI (2.37 life years) combined with PPS for chemotherapy from the company clarification response ([redacted] life years)

6.2.2. Subsequent treatment costs

The EAG applied subsequent treatment as the cost of a course on progression (to avoid inconsistency in the assumed time spent in the progression health state in the company's original formula as discussed in Section 4.2.8.2). This did not make a large difference to results.

In addition, the EAG assumed a mean time on treatment for NIVO + IPI and PEMBRO in the 2nd line of [redacted] based on the mean time on treatment in CM8HW (CSR Table 6.1-1) in the absence of data for previously treated patients. The direction of difference between 1st and 2nd line duration is unclear as 1st line patients may be expected to be fitter (longer duration) but there is no 2-year stopping rule applied in Blueteq for previously treated patients.

6.2.3. Subsequent treatment type

The EAG explored three scenarios for the type of subsequent treatment used per arm:

- Use of subsequent treatment data per the trials
- Use of subsequent treatment data per the trials with 42% of patients receiving an IO treatment receiving pembrolizumab monotherapy in line with the data supplied by Peter Clark
- Inclusion of encorafenib with cetuximab as a subsequent treatment for [redacted] of patients based on maximum possible use by all BRAF mutation positive patients[redacted]; Table 17 CS]

In all these scenarios current assumptions for effectiveness were maintained. The impact on effectiveness was explored in the next scenario.

6.2.4. Time to discontinuation for NIVO + IPI and chemotherapy

In line with what is stated in Doc B the EAG agreed that the TTD KM should be used to model time on treatment for NIVO + IPI and chemotherapy. Unfortunately, this was not presented in the model originally provided to the EAG. This model instead:

- Used PFS, the TTD KM data was not presented (it appeared to have been deleted by the modellers)
- The model artificially chopped off treatment at 2 years when the KM presented in Doc B demonstrates that some patients remain on treatment up to 40 months

The EAG received a corrected model following clarification questions which used the TTD KM data, this corrected model is used in the EAG base case. Additionally, the EAG implement a scenario where half-cycle correction was removed for drug costs as it was not appropriate given costs would be incurred in full on days that the drug is administered (and in particular all patients will have drug costs in cycle 1).

6.2.5. Time to discontinuation for PEMBRO

Here the EAG applied the HR from the NMA to TTP to the curve fit for NIVO + IPI to TTD to provide a more reasonable estimate of relative time on treatment as it would be expected that if PEMBRO was less effective in preventing progression the time on treatment would also be shorter.

6.2.6. Alternative curve fits for TTP

The EAG explored the use of the spline model supplied by the company in scenario analysis. The EAG tested the impact of changing the curve fit for both arms simultaneously.

6.2.7. Alternative NMAs

The EAG explored the use of the alternative NMAs supplied by the company in scenario analysis:

- Constant HR
- net1_-0.5_-0.5_111 FP NMA
- net1_-1_0_110 FP NMA

6.2.8. Treatment effect waning

The EAG assumed that treatment effect from the FP NMA only applies to the first 2 years of the model and after this timepoint hazards are equal for PEMBRO and NIVO + IPI in line with clinical expert advice to the EAG that an infinitely increasing treatment effect is not reasonable as response to IOs tends to occur in the first year of treatment and progression would then usually be observed during the 2 years of treatment or shortly after. At this timepoint 67 (out of 202) patients remain at risk for PFS in the NIVO + IPI arm of CM8HW, however, only 4 (out of 101) patients remain at risk on chemotherapy. Given this it is unsurprising that the FP NMA results differ considerably across different model fits as shown in Section 3.4.

We also test the impact of setting hazards equal at 1 year. At this timepoint 116 patients remain at risk for NIVO + IPI and 14 for chemotherapy.

Figure 22: Treatment effect on OS assuming treatment effect waning after 2 years shows that if hazards are equalized at 2 years the HR starts low [redacted] showing a significant early survival benefit of NIVO + IPI over PEMBRO. After two years, the treatment effect begins to wane, reflected in the rise of the HR. It eventually stabilises around [redacted] over the long term, suggesting that even when TTP is equalised the model assumes continue divergence of the OS curves albeit at a slower rate. Figure 23 shows that the analysis involves a steep jump in the hazard ratio for TTP from ([redacted]) to 1, this may not be completely realistic, however, given the

continued improved treatment effect that the EAG scenario translates to in OS setting the hazards equal at 2 years was considered reasonable.

Figure 22: Treatment effect on OS assuming treatment effect waning after 2 years

Figure 23: Treatment effect on TTP assuming effect treatment effect waning after 2 years

6.2.9. Alternative health state costs

The EAG amended health state costs based on clinical expert advice (Section 4.2.8.3) as shown in Table 32. The timepoints used are according to the model time horizon rather than time off treatment as the model structure does not allow for costs to be applied based on time since treatment stopped. This is considered to only result in minor inaccuracy. The EAG applied increased costs for subsequent lines of treatment using a payoff approach in line with how drug and admin costs are applied.

Table 32: EAG base case resource use per model cycle per health state

	On active treatment (any line)	Off active treatment (1 – 3 years)	Off active treatment (4 – 5 years)
Tumour marker test	0.23	1/3	1/6
Liver function test	1.15	1/3	1/6
CT scan	1/3	1/3	1/6
MRI scan	0.23	1/3	1/6

	On active treatment (any line)	Off active treatment (1 – 3 years)	Off active treatment (4 – 5 years)
Consultation outpatient appointment	Same time as IO treatment administration / start of chemotherapy cycle	1/3	1/6
Best supportive care	1/3 of patients – one model cycle for symptom management All patients – last model cycle prior to death	All patients – last model cycle prior to death	All patients – last model cycle prior to death

Abbreviations: EAG, External Assessment Group; CT computed tomography; MRI, magnetic resonance imaging; IO, immuno-oncology.

Health state costs - discounted	Company costs	EAG costs
PF NIVO+IPI	[redacted]	[redacted]
PD NIVO+IPI	[redacted]	[redacted]
PF PEMBRO	[redacted]	[redacted]
PD PEMBRO	[redacted]	[redacted]
PF Chemotherapy	[redacted]	[redacted]
PD Chemotherapy	[redacted]	[redacted]
Incremental NIVO+IPI vs PEMBRO	[redacted]	[redacted]
Incremental NIVO+IPI vs chemotherapy	[redacted]	[redacted]

The EAG consistently reported lower resource use and associated costs across all treatments and health states compared to the company's estimates. The largest differences were observed in the PD state for chemotherapy and in the PF states for both NIVO + IPI and pembrolizumab.

The discrepancy in the PF states for both NIVO + IPI and pembrolizumab can be explained by the unrealistic assumption in the company's model that patients would have two outpatient visits per cycle, regardless of whether they were on or off treatment or how long they had remained in the PF state. This assumption inflated the costs, particularly for NIVO + IPI. The difference in PD state costs is also large, particularly for chemotherapy, due to the company's inappropriate use of palliative care costs that were derived from a source reporting on the last 6 months of life to the entire time spent in PD regardless of whether patients were receiving active treatment or not.

Since the first assumption disproportionately affected NIVO + IPI, the use of the EAG's method to calculate costs slightly improved the cost effectiveness of NIVO + IPI compared to pembrolizumab and chemotherapy.

6.2.10. Wastage

The EAG used HSE data to model the impact of wastage using UK population weights in line with the company's response to clarification questions. This provided a more accurate estimate of the costs of ipilimumab as discussed in Section 4.2.8.1.

6.2.11. Chemotherapy split

The EAG explored the impact of the use of chemotherapy types per the adjusted trial analysis rather than the UK advisory board data used in the company base case. This increased the cost of chemotherapy due to the increased use of cetuximab-based regimens.

6.2.12. Improved utilities in PPS for chemotherapy

The EAG explored the use of an improved quality of life for patients starting on chemotherapy in PPS given these patients will be primarily going on to use IOs, whereas patients on NIVO + IPI will move on to chemotherapy. In this exploratory analysis an increase of [redacted] is assumed based on the difference between NIVO + IPI and chemotherapy observed in the PF health state.

6.2.13. Include AE utility decrements

The EAG explored the impact of inclusion of AE utility decrements given trial data are likely to under-represent their impact.

6.2.14. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.2.1 to 6.2.13. Each change was made individually first for the analyses comprising the EAG base case (Table 33) and then for exploratory scenario analysis on top of the EAG base case (Table 35).

6.3. EAG's preferred assumptions

At list price the EAG's preferred probabilistic base case ICERs are [redacted] and [redacted] when comparing to pembrolizumab and chemotherapy, respectively, while the preferred deterministic base case ICERs are [redacted] and [redacted]

Table 33: EAG's preferred model assumptions (list price)

Preferred assumption	Section in EAG report	Inc costs vs PEMBRO	Inc QALYs vs PEMBRO	Inc costs vs Chemo	Inc QALYs vs Chemo	ICER £/QALY vs PEMBRO	ICER £/QALY vs Chemo	+/- company base case vs PEMBRO	+/- company base case vs Chemo
EAG corrected company base case	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use HSE data to calculate wastage	6.2.10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No half-cycle correction for TTD	6.2.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use trial data for the split of treatments included in the chemotherapy comparator	6.2.11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use trial data to inform the subsequent treatments used	6.2.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS for patients after chemotherapy taken from exponential fit to CM142 Cohort 2 OS	6.2.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42% get PEMBRO rather than NIVO + IPI after chemotherapy based on data from Peter Clark	6.2.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs applied using payoff approach	6.2.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Section in EAG report	Inc costs vs PEMBRO	Inc QALYs vs PEMBRO	Inc costs vs Chemo	Inc QALYs vs Chemo	ICER £/QALY vs PEMBRO	ICER £/QALY vs Chemo	+/- company base case vs PEMBRO	+/- company base case vs Chemo
PEMBRO TTD calculated by applying TTP HR to NIVO + IPI TTD curve	6.2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards for PEMBRO and NIVO + IPI set equal at 2 years	6.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use based on EAG clinical expert input	6.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative impact of EAG base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; HSE, Health Survey England; TTD, Time-to-discontinuation; Inc, incremental; Chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab; PAS, patient access scheme; PEMBRO, pembrolizumab; QALY, quality adjusted life-years; PPS post-progression survival; CM, CheckMate; TTP, time-to-progression; HR, hazard ratios

Table 34: EAG probabilistic base case (list price)

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER £/QALY	Probability of being CE
Comparison to pembrolizumab						
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO						
Comparison to chemotherapy						
NIVO + IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy						

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; Inc, incremental; CE, cost effective

Table 35: EAG's exploratory analyses (list price)

Preferred assumption	Section in EAG report	Inc costs vs PEMBRO	Inc QALYs vs PEMBRO	Inc costs vs Chemo	Inc QALYs vs Chemo	ICER £/QALY vs PEMBRO	ICER £/QALY vs Chemo	+/- company base case vs PEMBRO	+/- company base case vs Chemo
EAG base-case	*6.1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude BSC costs	*6.2.9*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO OS equal to NIVO + IPI OS	*6.2.1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS for chemotherapy based upon the absolute difference in LYs from TA716	*6.2.1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42% get PEMBRO and reduced PPS for subsequent PEMBRO vs subsequent NIVO + IPI using data from TA716	*6.2.3*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Equal PPS to TA709 for PEMBRO and NIVO + IPI (2.37 life years) combined with PPS for chemotherapy from CM142	*6.2.1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazards for PEMBRO and NIVO + IPI set equal at 1 year	*6.2.1*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion of encorafenib with cetuximab as a subsequent treatment for 38% of patients	*6.2.3*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Section in EAG report	Inc costs vs PEMBRO	Inc QALYs vs PEMBRO	Inc costs vs Chemo	Inc QALYs vs Chemo	ICER £/QALY vs PEMBRO	ICER £/QALY vs Chemo	+/- company base case vs PEMBRO	+/- company base case vs Chemo
Alternative Fractional Polynomial NMA 1	*6.2.7*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative Fractional Polynomial NMA 2	*6.2.7*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant hazards NMA	*6.2.7*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTP for both arms uses two knot spline model	*6.2.6*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Improved utilities in PPS for chemotherapy	*6.2.12*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Include AE utility decrements	*6.2.13*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CM, CheckMate; EAG, External Assessment Group; HSE, health survey England; ICER, incremental cost-effectiveness ratio; IO, immune-oncology; PEMBRO, pembrolizumab; QALY, quality adjusted life year; TTD, time to discontinuation, Inc, incremental; Chemo, chemotherapy; BSC, best supportive care; PPS, post-progression survival; LY, life years; TA, technology appraisal; TTP, time-to-progression; OS, overall survival; IPI, ipilimumab; NIVO, nivolumab; CM, checkmate; NMA, network meta-analysis; AE, adverse events

6.4. Conclusions of the cost-effectiveness section

The company submitted a de novo economic model and ICER estimates for NIVO + IPI in comparison to PEMBRO and chemotherapy. However, the EAG identified several limitations in the company's base case model.

Key issues included: 1) the absence of OS data from the CM8HW trial. This presented challenges to validation of the accuracy of projections and added further complexity to the comparison between treatments, 2) concerns regarding the transitivity assumption in NMA and plausibility of long-term estimates leading to uncertainty regarding the effectiveness compared to pembrolizumab, 3) uncertainties related to survival after disease progression, the treatment pathways that follow and the costs and quality of life impact associated with them and 4) uncertainty regarding the length of time patients are treated with pembrolizumab, and 5) the cost of disease management.

To address these issues and clarify uncertainties, the EAG made the necessary corrections and conducted a range of scenario analysis. Some of the errors in the company's base case ICERs included issues like drug costing errors, errors in the Dirichlet distribution and AEs distribution in subsequent treatment in the PSA, and minor mistakes in age-adjusted utility values. Those errors, however, had minor impact on the ICER

The EAG has also conducted a series of exploratory analyses of its preferred assumptions on top of the company base case. A number of these revisions led to substantial shifts from the company's base case. The EAG's use of trial data (rather than the advisory board data used by the company) to inform subsequent treatment types, resulted in a [redacted] increase in the ICER versus chemotherapy. Additionally, the use of the payoff approach to calculate the cost of subsequent treatments introduced another substantial shift, increasing the ICER versus chemotherapy by [redacted]. In contrast, the ICER versus pembrolizumab appeared less sensitive to most of the EAG's assumptions, although certain assumptions still had a notable impact. For example, the EAG preferred assumption for pembrolizumab's TTD, calculated using TTP hazard ratios, resulted in a [redacted] increase from the company's base case ICER. The combination of these changes resulted in the EAG's preferred probabilistic base case ICERs of [redacted] versus pembrolizumab and [redacted] versus chemotherapy at list price. The corresponding deterministic ICERs stand at £[redacted] and [redacted], respectively. These ICERs should not be over-interpreted as a large number of treatments have discounts either via a PAS or CAA.

The EAG's exploratory analysis tested several assumptions and parameters on top of its base-case, especially where cost effectiveness results were likely to show the greatest sensitivity.

The most impactful of these was assuming equal overall survival for NIVO + IPI and PEMBRO, which led to a marked increase in the ICER to [redacted]. This highlighted the impact of survival differences between the two arms in driving cost effectiveness. Given that no OS data were supplied for the CM8HW trial to validate the company's assumptions, and that validation exercises found that the model underpredicted outcomes for PEMBRO in the long-term while overpredicting outcomes for NIVO + IPI in the long-term when compared to CM142, the EAG consider equal OS a plausible scenario.

Another major shift in the ICER occurred when the EAG modelled post progression survival for chemotherapy based on the absolute difference in life years from second line treatments assumed in TA716 (the appraisal of NIVO + IPI as a second-line treatment). This resulted in a large rise in the ICER versus chemotherapy to [redacted]. Use of PPS estimates from TA709 (the first line appraisal of pembrolizumab) also substantially increased the ICER. PPS was a lot lower in this appraisal. However, the treatment pathway in the KN-177 trial used for this appraisal may be expected to be more reflective of current practice as IOs were not commercially available as second-line treatments when this trial was run.

The two knot spline scenario for time to progression resulted in an even higher ICER. This was particularly the case against chemotherapy, where assuming a shorter TTP for NIVO + IPI, whilst modelling PPS based upon NIVO + IPI data from CM142, resulted in chemotherapy gaining more total LYs than NIVO + IPI. This led to a sharp increase in the ICER to [redacted]

Lastly, the scenario of improved utilities for patients undergoing chemotherapy in PPS resulted in another substantial ICER rise, this time to [redacted]. The assumption was that patients transitioning from chemotherapy to IO treatments may experience better quality of life than those on NIVO + IPI, who are moving to chemotherapy. This was a reasonable scenario which shows that cost effectiveness results are highly sensitive to this area of uncertainty

Additionally, in the subgroup analysis presented by mutation status. The company's adjustment to the chemotherapy comparator focused only on cost and did not amend

baseline or relative risks of events. As a result, the EAG considered these adjustments of limited use. Furthermore, while data from the CM8HW trial suggested that the treatment effect for NIVO + IPI was likely to be consistent across subgroups, the baseline risk differed for the BRAF mutation subgroup. This group showed a higher median PFS compared to the total centrally confirmed population [redacted] Consequently, this improved PFS for standard chemotherapy suggested a lower likelihood of cost-effectiveness for NIVO + IPI in this subgroup.

In conclusion, some important uncertainties remain. The EAG's adjustments and analysis aimed to reflect more realistic assumptions, but the cost effectiveness of NIVO + IPI is still highly sensitive to assumptions around survival, subsequent treatments, and patients' quality of life. These uncertainties need to be considered in decision making, as they have a significant impact on the cost effectiveness results, especially when comparing NIVO + IPI to chemotherapy.

7. QALY MODIFIER

Using the tool supplied by Schneider et al (2021)[43] the EAG calculated the proportional and absolute QALY shortfall (Table 36). NIVO + IPI does not meet the criteria to quality for a severity modifier.

Table 36: Calculation of QALY shortfall

	vs PEMBRO	**vs chemotherapy**
Remaining QALYs without the disease	12.37	12.37
Remaining QALYs with the disease	[redacted]	[redacted]
Absolute shortfall	[redacted]	[redacted]
Proportional shortfall	[redacted]	[redacted]

Abbreviations: QALY; quality adjusted life-years; PEMBRO, pembrolizumab.

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Single Technology Appraisal

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

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 the end of **16 September 2024** 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 information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Overall survival

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, page 17 The report states "The company said that OS data were not mature and therefore decided not to supply any OS data from the pivotal trial" Section 3.2.2.1 page 37 The report states "In response to clarification question A15, the company declined to provide these data as the trial had not reached maturity." Section 3.2.3 Page 51 The company said that OS data were not mature and therefore decided not to supply any OS data from	Relevant sections should be updated to reflect that BMS does not currently have access to OS data.	This is factually incorrect. CheckMate 8HW employs a pre-specified statistical testing hierarchy based on the occurrence of a predetermined number of events to ensure statistical validity and meaningful conclusions. As noted in the CheckMate 8HW CSR (Section 4.5.1), this study used an independent data monitoring committee (DMC) to provide an independent evaluation of the interim analysis results. Statistical analyses for the DMC were performed by an independent statistical group. When the DMC notified BMS that the tested primary endpoint achieved the pre-specified significance level and the unblinding threshold, the BMS study team was unblinded to the concluded part of study	The EAG notes that trial design is the company's choice and it is a direct consequence of this design that OS data are not available for this appraisal. The company should note the importance of OS data for oncology appraisals and therefore the importance of ensuring these data are available for the submission. The EAG has in its experience not had such issues with OS data availability with submissions from other companies and has frequently seen ad-hoc OS analyses provided for policy purposes. While the EAG does not consider its original text

the pivotal trial (clarification response A21). Section 3.6 Page 75 The company said that OS data were not mature and therefore decided not to supply any OS data from the pivotal trial.		results and data, including data for efficacy (PFS, PFS2, and RFS), PK, biomarkers, safety, immunogenicity and PRO. All other endpoints remain blinded to the BMS study team. Analysis to inform regulatory submissions and HTA submission was conducted using patient-level data that did not include OS data. It should be clarified that maturity of OS was not used to determine whether or not to provide the data. This data is not available to BMS, regardless of maturity. We anticipate the OS data becoming avail as part of the final database lock in [redacted]. The impact of the unrevised text is to imply to stakeholders, including the NICE committee members, that BMS is hiding information and being uncooperative.	to be factually inaccurate, it has made revisions to the text for clarity.

Section 1.4, page 18. Page 51 and page 77. The report states: Provision of an ad hoc analysis confidentially, which could be an analysis that has been submitted to MHRA, EMA or FDA.	This statement should be amended to read: “Provision of an ad hoc analysis confidentially, which could be an analysis relevant for submission to MHRA, EMA or FDA, if requested.	[redacted] BMS are not able to provide this data at present. In the future, there could be a condition/commitment to provide secondary endpoints (such as OS) if the [redacted] approval states this. The planned [redacted] submission to the MHRA will be based on the [redacted] will be provided in support of the application. The impact of the unrevised text is to imply to stakeholders, including the NICE committee members, that BMS is hiding information and being uncooperative.	[redacted]
Section 1.4, page 17, Section 3.2.3 Page 50, Section 3.6 Page 75	This statement should be amended to read: “The EAG noted that at the time of the interim analysis (12 October 2023), the information fraction for the	The cited information fraction relates to PFS per BICR. This cannot be assumed to relate to other endpoints. The rate of	This is not a factual error and the EAG believe this is clear in context. It is the EAG’s

The report states: “The EAG noted that at the time of the interim analysis (12 October 2023), the information fraction was 80%, suggesting that OS data at this point in time would likely closely parallel the final OS data.”	primary endpoint (PFS per BICR) was 80%.”	information accrual is a function of both hazard and remaining at-risk population size, and the total amount of information left to be gained is proportional to the remaining at-risk population size. At final analysis, the incremental information gained for OS may be greater than the incremental information gained for PFS from this interim analysis timepoint, due to the larger at-risk population resulting in a more rapid average rate of information accrual (i.e. larger absolute number of events per unit time) than in the more depleted pre-progression population.	opinion that the information about PFS by BICR would in fact warrant the assertion.
Section 3.2.3 Page 51 The report states: “The EAG also noted that deaths are a safety endpoint in this trial and therefore the company has access to death data.”	Relevant sections should be updated to reflect that BMS does not currently have access to OS data.	As noted above, BMS does not have access to OS data at present. Analyses to inform regulatory submissions and HTA submission was conducted using patient-level data that did not include OS data.	This is not a factual error. Deaths are in fact a safety endpoint and to the extent these were presented, death data are available to the company.

Section 3.2.3 Page 54 The report states: “The company stated that it would only provide data from secondary outcomes once the trial was complete, rather than in interim analyses.“	Relevant sections should be updated to reflect that BMS does not currently have access to data for some secondary outcomes.	As noted above, BMS does not have access to data for other endpoints at present. This data will be provided in line with pre-specified protocol defined analysis criteria.	This is not a factual error.

Issue 2 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 1.7 Table 35 Page 25 and Section 6.3 Table 35 Page 141 BMS believe that the row titled “Resource use based on EAG clinical expert input” includes assumptions for row above (“Hazards for PEMBRO and NIVO + IPI set equal at 2 years”)	The row should be checked and amended if incorrect	Factual accuracy	Amended, this was a copy paste error for this scenario. No changes were made to the model.
Page 28	This statement should be amended to read: [redacted]	This is a factual inaccuracy and is significant for	The information in the EAG report

[redacted]	[redacted]	providing timely guidance to prescribers.	accurately portrays the information in the CS (Table 2). The EAG has updated its report based on this new information.
Page 39 "CM142 did not include participants with ECOG 2."	This statement should be amended to read: "CM142 and CM8HW did not include participants with ECOG 2."	While this is true, it implies that CM8HW did allow participants with ECOG PS=2. Inclusion criteria for CM8HW were ECOG PS = 0 or 1, and no 1L patients were enrolled in any arm with ECOG PS >1 or unknown. The error should be amended to aid clarity and avoid ambiguity.	The EAG has updated this for additional clarity, while agreeing with the company that the initial statement was not factually incorrect.
Page 40 table 8, column 1 row 12. "ECOG PS, n (%) ≥ 1."	This statement should be amended to read: "1".	No 1L patients were enrolled in any arm with ECOG PS >1 or unknown. The error should be amended to aid clarity and avoid ambiguity.	The EAG has amended this for clarity.

Page 46, bullet point 4. Patients who received subsequent anti-cancer therapy or crossed over to receive treatment aligned to another arm of the trial were censored at the date of the last evaluable tumour assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy/crossover.	This statement should be amended to read: "Patients who received subsequent anti-cancer therapy or crossed over to receive treatment aligned to another arm of the trial, prior to documented progression, or with no documented progression, were censored at the date of the last evaluable tumour assessment conducted on or prior to the date of initiation of the subsequent anti-cancer therapy/crossover.	The error should be amended to aid clarity.	The EAG did not consider this to be a factual error, however has revised as requested for additional clarity.
Page 49. "The company indicated that the earliest it will provide NIVO monotherapy results would be [redacted]	This statement should be amended to read: "The company indicated that the earliest it will provide NIVO monotherapy results would be [redacted]	The EAG have identified a typographical error in the response to clarification question B4. The correct date is [redacted]	The EAG has amended as requested, reflecting the error made by the company in the clarification response.
Page 56, table 11 The table title states that it displays CM8HW PFS in the centrally confirmed	Update total row with results/data from the centrally confirmed population. PFS Nivo and Ipi = NR (38.4-NE), PFS for chemo is 5.9 (4.4-7.8). HR = 0.21 (0.13-0.35)	The error should be amended for accuracy.	Amended as requested, including change to markup.

population. However, the data in the “Total” row are for the ITT population.			
Page 81, 4.2 “At clarification question response the company submitted a further seven model files for the adult population over a week late (one for each scenario) and following the EAG noting an error in the company model the company then supplied a further 54 model files the week the EAG report was originally due (one for each scenario analysis conducted by the company).	This statement should be amended to read: “Following clarification question responses we requested further information on TTD data that was missing from the company model. The company submitted a further seven model files for the adult population within a week (one for each scenario). Following the EAG noting an error in the company model the company then supplied a further 54 model files the week the EAG report was originally due (one for each scenario analysis conducted by the company)”.	BMS did not provide late clarification responses. BMS responded to a request for further information that was issued after the agreed timeline for clarification questions. The EAG also added an additional question at the clarification question meeting to those that had been issued previously by NICE. BMS agree with the EAG that providing them with multiple files is not best practice. Due to the very tight timelines for the EAG and BMS, we opted on this occasion to share results and amendments as soon as possible rather than delay to create one master file.	This is not a factual inaccuracy. The responses supplied by BMS to clarification questions did not contain an updated model for the new scenarios provided. This should be standard practice to include. The Excel files took over a week for the EAG to obtain.

<table>
<tr>
<td></td>
<td></td>
<td>The impact of the unrevised text is to imply to stakeholders, including the NICE committee members, that BMS is being uncooperative. BMS have made every effort to accommodate EAG requests in a timely manner.</td>
<td></td>
</tr>
<tr>
<td>EAG report Section 4.2.2.3 Page 85 and Section 4.2.6.2 Page 94

There appears to be inconsistency in how the percentage of deaths occuring within the progression endpoint are calculated within the following statement: Death (as opposed to progression) events occured in [redacted] of the NIVO + IPI arm and [redacted] of the chemotherapy arm in CM8HW (CSR Table 7.1.1-1) and 11.1% of the PEMBRO arm and 17.5% in the chemotherapy arm after</td>
<td>The statement should be updated to use a consistent population, as depicted in the below table. Additionally, the statement should be amended to use CheckMate 8HW ITT population data or should clearly denote which population is being compared.

Table. Deaths occurring as part of PFS endpoint
<table>
<tr><td>Proportion of deaths within PFS endpoint</td><td>In all patients</td><td>In patients with PFS event</td></tr>
<tr><td colspan="3">CheckMate 8HW ITT</td></tr>
<tr><td>NIVO + IPI</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>CheckMate 8HW data used to inform the statement is calculated as the number of deaths in the PFS endpoint divided by the number of PFS events. KEYNOTE-177 data is calculated as the number of deaths in the PFS endpoint divided by the number of patients in the ITT population.

Additionally, the population should ideally be like for like (i.e. ITT vs ITT) when comparing. If the centrally confirmed population from CheckMate 8HW is preferred, this should be stated.</td>
<td>Thank you for this helpful comment and supplying data for the ITT population for CheckMate 8HW. The figures have now been amended to use the ITT populations from both trials and to use deaths as a proportion of patients with a PFS event.</td>
</tr>
</table>

median follow-up of 28.4 months in KN177.[27]	CHEMO [redacted] [redacted] CheckMate 8HW centrally confirmed NIVO + IPI [redacted] [redacted] CHEMO [redacted] [redacted] KEYNOTE-177 PEMBRO 17/153 (11.1%) 17/84 (20.7%) CHEMO 27/154 (17.5%) 27/113 (23.9%)		
Page 95, 4.2.6.3. The model predicts observed PFS well in CM8HW for NIVO + IPI but underpredicts observed PFS for chemotherapy after 6 months. This indicates that there is a systematic bias in favour of NIVO + IPI.	We believe the ERG may have made a typo. The text should read as "The model predicts observed PFS well in CM8HW for NIVO + IPI but overpredicts observed PFS for chemotherapy after 6 months. This indicates that there is a systematic bias in favour of NIVO + IPI".	Accuracy.	Amended, thank you.
Section 5.2.3 Page 123 and Table 26 Page 126 BMS has been unable to reproduce the outcomes for use of trial-based subsequent treatment which increased the ICER to	The row should be checked and amended if incorrect	Factual accuracy	Amended, this was a copy paste error for this scenario. No changes were made to the model.

<table>
<tr><td>£13,395 vs chemotherapy and led to a non-dominant result vs PEMBRO (both of which are costed at list price)</td><td></td><td></td><td></td></tr>
<tr><td>Section 5.2.3 Table 26 Page 126-127

BMS has been unable to identify the source for provided outcomes for the TA709 utilities scenario analysis</td><td colspan="2">BMS believe the values in the table should be as provided in the updated table below, based on the submission addendum.

<table><tr><th colspan="6">TA709 utilities</th></tr><tr><td>NIVO + IPI</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>PEMBRO</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Chemotherapy</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>The scenario in question used values from the KN-177 trial in the provided company model sheet “Trial and TA709 Utilities” range C5:F7.

This inaccuracy was caused by a discrepancy between the company model and the submission appendices. Nonetheless, the EAG re-ran the scenario using the values in the submission (Table 8 in Appendix H) and updated the report accordingly.</td></tr>
</table>

Issue 3 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.2.2.1 Page 37 The report states "(mFOLFOX or FOLFIRI ± bevacizumab or cetuximab)", which may be subject to confusion	The statement should be updated to be clearer, such as ""(fluoropyrimidine regimen [mFOLFOX or FOLFIRI] with or without bevacizumab or cetuximab)".	This statement could be misinterpreted.	The EAG does not consider this to be a factual error but has made the suggested edit for additional clarity.
Section 3.2.2.5 Page 44 The report states "OS by investigator or BICR (not clearly stated in CS if it was one either/or endpoint or two separate endpoints)"	The statement should be updated to reflect that OS is an objective endpoint that does not require external assessment.	This statement should be updated for clarity.	Amended for clarity, as requested.
Section 3.2.2.5 Page 45 The report states: Furthermore, the EAG noted the immaturity of a sample size of 45 in CM142, of which MSI-H status was only centrally confirmed in 10 of these cases.	The statement should be updated to read: Furthermore, the EAG noted the immaturity of a sample size of 45 in CM142, of which MSI-H status was only centrally confirmed in 10 of the 12 patients assessed; the remaining 33 patients were not assessed.	This statement is misleading as it implied that 35 patients were MSS.	Amended for clarity, as requested.

Section 3.2.2.5 Page 47 The report states: KM curves for PFS and OS were generated. PFS and OS rates at specific timepoints were estimated using KM estimates and associated two-sided 95% CIs were calculated	The statement should be updated to read: KM curves for PFS were generated. PFS rates at specific timepoints were estimated using KM estimates and associated two-sided 95% CIs were calculated. OS will be assessed using the same approach when available.	The statement implies that OS has been assessed. As stated above, OS data are not available to BMS. However, these methods are pre-specified for OS analysis.	Amended for clarity, as requested.
Section 3.2.2.5 Page 47 The report states: Analysis was not presented using the EMA definition for subsequent treatment.	The statement should be updated to read: The CS did not present analysis using the EMA definition for subsequent treatment; however, this was presented in response to CQ.	Outcomes for this analysis are provided in response to question A29 (page 38-40). Data are described on page 53 of EAG report.	Revised as requested.
Section 3.2.2.5 Page 48 The report states: TTNT is available for both CM8HW and CM142. It was, however, not listed in the summary of endpoints in the CS or discussed in the CSRs, meaning details of how it was assessed were not available.	The statement should be updated to read: TTNT was provided in response to an EAG clarification question, but was not a pre-specified endpoint, meaning details of how it was assessed were not available.	TTNT was an ad hoc analysis provided in response to an EAG clarification question but was not pre-specified.	Revised as requested.

Section 3.2.3 Page 51 and Section 3.6 Page 76 The report states: EAG note that of the 5 appraisals listed in the CS as being ones where OS data was not provided: • OS data was provided in TA709: a competitor submission in the same indication with a similar level of data maturity at the time of submission • OS data was provided in TA716 • OS data was provided in TA400 after the initial submission prior to the Committee meeting (see page 879 of the Committee papers for example)	This statement should be deleted.	This statement mischaracterises the context in which these appraisals are listed. The company submission states: Additionally, it is common in IO appraisals in dMMR/MSI-H mCRC that median OS is not reached, as in TA716 (NIVO + IPI in previously-treated dMMR/MSI-H mCRC) and TA709 (PEMBRO in previously untreated dMMR/MSI-H mCRC);[1,74] in TA716, it was considered that awaiting OS data would necessitate significant delay in patients being able to access a treatment which would fulfil an unmet need, and which had demonstrated efficacy.[74] This has also been the case in appraisals of NIVO + IPI in other indications, such as for the treatment of advanced melanoma (TA400).[136]	The EAG does not consider the listing of these appraisals and information about how OS was handled in these appraisals to be factually inaccurate.

		In summary, the company submission makes the point that OS evidence is commonly immature during HTA, as evidenced by these HTAs. It does not claim that OS was not available.	
Section 3.4.3 Page 72 The report states: The constant-hazard network meta-analysis was presented as another indirect treatment comparison scenario analysis for the primary endpoint.	The statement should be updated to read: The constant-hazard network meta-analysis was presented for completeness and as a validation exercise, noting that this should be interpreted with caution.	For clarity, the CS notes that this analysis should be interpreted with caution, as the PHA is violated. However, the approach is specifically presented for completeness and as a validation exercise.	Additional clarification added, as requested.
Section 4.2.6.4 Page 96 The report states: the EAG are aware of other sources (e.g. KN-177) which have not been considered.	The statement should be updated to read: the EAG are aware of other sources (e.g. KN-177) which have not been considered, although limitations to access of these data sources are noted.	BMS is unable to analyse post-progression survival from KN-177 as patient-level data and outcomes for this endpoint are not available. An approximation may be developed but may not be considered as reliable as a trial for which patient-level data is available.	Appendix O of the company submission mentions that cumulative hazard curves from the pembrolizumab submission to CADTH were digitised and transformed to estimate post-progression survival for both

			PEMBRO and chemotherapy. These estimates were then used in an exploratory analysis. Several studies have validated the method, finding it to be a robust approach with less than 1% mean error in survival probability. The unavailability of patient-level data should not have prevented the use of data from KN-177.
Section 4.2.6.4 Page 95 The report states: The scenario analysis presented using data from CM142 Cohort 2 (2L+ NIVO + IPI) to inform PPS after chemotherapy assumes an exponential fit and appears to actually use PPS data from Cohorts 2 and 3 as the coefficient is identical to what was in the model previously.	This statement should be amended to read: The scenario analysis presented using OS data from CM142 Cohort 2 (2L+ NIVO + IPI) to inform PPS after chemotherapy assumes an exponential fit.	The CM142 cohort 2 OS data inputs were provided in the base case model version. However, it is worth noting that some extrapolations provide implausibly long survival outcomes, with LYs for NIVO + IPI 2L predicted to be longer than LYs for NIVO+IPI 1L.	Thank you for the confirmation that the coefficient is indeed correct. Report amended. The EAG agree that scenarios based upon the data supplied include the possibility of similar survival for the sequence of chemotherapy followed by NIVO+IPI vs

Similar statements are included elsewhere, including Section 4.2.8.2 Page 112 and Section 6.2.1 Page 134			NIVO+IPI followed by chemotherapy.
Section 4.2.8.2 Page 112 The EAG is unclear of the rationale for the exclusion of cetuximab and do not agree as this is used in the UK in the second line setting according to clinical expert advice received by the EAG.	This statement should amended or deleted.	TA242 states that Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. Cetuximab may be used in combination with encorafenib (TA668). However, encorafenib was not used in CheckMate 8HW, so these patients were excluded.	Amended as requested to add the company rationale for exclusion, however, this is not a valid reason to exclude this combination and highlights an area of lack of generalisability of the trial data to the NICE decision problem.
Section 6.2.4 Page 135 This section describes the TTD KM error addressed by the addendum.	The section should be amended to describe the problem but make it clear that the model has been corrected following CQs.	At present, it is not clear that the results presented have this error corrected.	Amended for clarity, as requested.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 29, table 4, population row, column 3.	Details of the confidential draft marketing authorisation have not been redacted.	As per NICE scope. It is noted that the company revised its intended population to be [redacted], following a change in the expected marketing authorisation (MA).	The EAG had not been advised that the change of intended marketing authorisation was confidential. Marking amended as requested.
Page 29, table 4, population row, column 4.	Details of the confidential draft marketing authorisation have not been redacted.	The [redacted] was to reflect the expected MA. The scope was not revised, as the appraisal had already commenced.	As above.
Page 29, table 4, population row, column 5.	Details of the confidential draft marketing authorisation have not been redacted.	The company decision problem aligned with the NICE scope. The EAG report focuses on the [redacted], following advice from NICE that the company's intended MA had been revised to [redacted]	As above.
EAG report Section 4.2.2.3 Page 85 and Section 4.2.6.2 Page 94	Commercially confidential data from the CM8HW CSR has been quoted and not redacted.	Death (as opposed to progression) events occured in [redacted] of the NIVO + IPI arm and [redacted] of the chemotherapy arm in CM8HW (CSR Table 7.1.1-1)	Amended as requested.

		and 11.1% of the PEMBRO arm and 17.5% in the chemotherapy arm after median follow-up of 28.4 months in KN177.[27]	
Page 94, 4.2.6.2	Commercially confidential data from the CM8HW CSR has been quoted and not redacted.	The EAG considered this to be flawed as data from both CM-8HW and KN-177 demonstrate a reasonable proportion of patients experiencing a death event as part of PFS early on in the trial 11.1% - [redacted]%.	Amended as requested.

(Please add further lines to the table as necessary)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab plus ipilimumab for untreated metastatic colorectal cancer with high microsatellite instability or deficient mismatch repair [ID1136]

Summary of CheckMate 8HW Interim Analysis 1b November 2024

January 2025

File name	Version	Contains confidential information	Date
	V1	Yes	6th January 2025

Summary of CheckMate 8HW Interim Analysis 1b – November 2024 (latest database lock)

As noted in the company submission and clarification questions, the CM8HW trial employs a pre-specified statistical testing hierarchy based on the occurrence of a predetermined number of events to ensure statistical validity and meaningful conclusions. BMS and all stakeholders are blinded to all data until the prespecified database locks (DBL) are completed and analysed.

The BMS submission (ID1136) is based on interim analysis 1, the November 2023 DBL. In the interests of transparency, we are sharing the key results of the second and latest analyses, September 2024 DBL, with NICE.

Please treat all results as commercial in confidence.

Results.

1. [redacted]

Figure 1: Progression-Free Survival per BICR (Primary Definition) for NIVO + IPI vs NIVO - All Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC

Number of subjects at risk
Arm A: NIVO
[redacted]
Arm B: NIVO = IPI
[redacted]
--Δ-- Arm A: NIVO (events [redacted]), median and 95% CI : [redacted]
--|-- Arm B: NIVO + IPI (events [redacted]), median and 95% CI : [redacted]
Arm B: NIVO + IPI vs. Arm A: NIVO – hazard ratio (95% CI): [redacted]
Arm B: NIVO + IPI vs. Arm A: NIVO – hazard ratio (99.05% CI): [redacted]
p-value: [redacted]

Statistical model for HR and p-value: Stratified Cox proportional hazard model and stratified log-rank test by tumour sidedness (left vs. right) and prior lines of therapy (0, 1, ≥ 2) as entered into the IRT.
Symbols represent censored observations.

2. [redacted].

Table 1: Best Objective Response Rate per BICR for NIVO + IPI vs NIVO - All Randomized Subjects with Centrally Confirmed MSI-H/dMMR mCRC

	Number of Subjects (%)	
	Arm A: NIVO N=xxx	**Arm B: NIVO + IPI** N=xxx
Confirmed best overall response		
Compete response (CR)	[redacted]	[redacted]
Partial response (PR)	[redacted]	[redacted]
Stable disease (SD)	[redacted]	[redacted]
Progressive disease (PD)	[redacted]	[redacted]
Unable to determine (UTD)	[redacted]	[redacted]
Nor reported	[redacted]	[redacted]
Objective response rate (1)	[redacted]	[redacted]
(95% CI)	[redacted]	[redacted]
Disease control rate (1)	[redacted]	[redacted]
(95% CI)	[redacted]	[redacted]
Difference of Objective response rate (2, 3)		[redacted]
(95% CI)		[redacted]
(99.4% CI)		[redacted]
Estimate of odds ratio (3, 4)		[redacted]
(95% CI)		[redacted]

(99.4% CI)	[redacted]
P-value	[redacted]

Per RECIST 1.1, confirmation of response is required at least 4 weeks after the initial response.
(1) ORR (CR+PR) and DCR (CR+PR+SD at least 12 weeks), CI based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Arm B - Arm A) based on Cochran-Mantel-Haenszel
(CMH) method of weighting.
(3) Stratified by tumour sidedness (left vs. right) and prior lines of therapy (0, 1, ≥ 2) as entered into the IRT.
(4) Strata adjusted odds ratio (Arm B over Arm A) using Mantel-Haenszel method.
(5) 2-sided p-value from stratified CMH Test. Boundary for statistical significance p-value < 0.006.

3. [redacted]

Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]

A Single Technology Appraisal

Addendum: Comparison of Updated Kaplan Meier Data to Model Predictions

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Rider on responsibility for document	**The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors**

This report should be referenced as follows	**This report should be referenced as follows: Barnish et al.** Nivolumab with ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]: A Single Technology Appraisal**. Peninsula Technology Assessment Group (PenTAG), 2024.**

All CIC (Commercial in Confidence) data has been highlighted in blue and underlined, all AIC (academic in confidence) data is highlighted in yellow and underlined

COMPARISON OF UPDATED KAPLAN MEIER DATA TO MODEL PREDICTIONS

The EAG received the updated 5-year Kaplan-Meier (KM) plot of progression-free survival (PFS) based on the primary definition and assessed by blinded independent central review (BICR) for all randomized subjects with centrally confirmed dMMR/MSI-H status in the nivolumab arm and the nivolumab plus ipilimumab arm.

To evaluate the model's external validity, the EAG compared the model projections to the empirical data not used in model construction. This was done by overlaying the 5-year PFS KM curve from the trial with the 5-year PFS health state occupancy estimates in the model (Figure 1).

Figure 1: Fit of model to observed data

Nivolumab plus ipilimumab observed results vs model projections

The KM curve for the nivolumab plus ipilimumab arm appears to align closely with the model's health state occupancy projections for nivolumab plus ipilimumab with the model slightly underestimating PFS compared to the empirical data for the majority of the observed dataset and overestimating the probability of PFS compared to KM results at the very end of the data when there were less than [redacted] of patients remaining. Consequently, discrepancies at the end of the KM curve likely reflect the inherent variability in the KM data rather than a fundamental issue with the model.

Nivolumab monotherapy observed results vs pembrolizumab model projection

Since nivolumab and pembrolizumab are often considered clinically similar and to have similar effectiveness (both being PD-1 / PD-L1 inhibitors) it is concerning that significant deviations are seen here between nivolumab's observed KM results and pembrolizumab model projections. This suggests the model under-predicts pembrolizumab's PFS and inflates the apparent clinical advantage of nivolumab plus ipilimumab in the analysis, leading to the conclusion that the ICER versus pembrolizumab currently presented is considerably lower than would be expected if data for nivolumab from the trial was used as a proxy for pembrolizumab's effectiveness and that the current modelled estimates do not provide an estimate of incremental cost-effectiveness versus pembrolizumab that is robust enough for decision making.

Impact of difference in projections

The EAG conducted an exploratory analysis to determine the impact of the difference in modelled projections for pembrolizumab and observed results for nivolumab on the ICER. Application of a hazard ratio of [redacted] to the initial projected time to progression curve for pembrolizumab results in a reasonable visual fit to the data for nivolumab (Figure 2).

Figure 2: Fit of model to observed data in EAG exploratory analysis

In the corrected company base case applying the new HR does not have a major impact on the ICER due to the way that costs were applied in the original model (i.e. linked to the minimum of TTD for nivolumab plus ipilimumab and TTP for pembrolizumab rather than assuming [redacted]). In the EAG base case, however,

increased effectiveness of pembrolizumab in line with the observed data for nivolumab monotherapy leads to an ICER above the NICE threshold of £20-30,000 per QALY.

Table 1: Impact of exploratory analysis on the cPAS ICER

	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER £/QALY
Corrected company base case					
NIVO + IPI	[redacted]	[redacted]	-	-	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corrected company base case + HR of [redacted] applied to PEMBRO TTP					
NIVO + IPI	[redacted]	[redacted]	-	-	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case					
NIVO + IPI	[redacted]	[redacted]	-	-	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case + HR of [redacted] applied to PEMBRO TTP					
NIVO + IPI	[redacted]	[redacted]	-	-	-
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]