Medicinrådet

Bilag til Medicinrådets vurdering af nivolumab i kombination med ipilimumab til behandling af patienter med defekt mismatch repair system eller høj mikrosatellitinstabilitet tyk- og endetarmskræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nivolumab i kombination med ipilimumab
2. Forhandlingsnotat fra Amgros vedr. nivolumab i kombination med ipilimumab
3. Ansøgers endelige ansøgning vedr. nivolumab i kombination med ipilimumab

Bristol Myers Squibb
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Virum d. 29.08.25

Til Medicinrådet

Bristol Myers Squibbs tilbagemelding på udkast til vurderingsrapport for nivolumab + ipilimumab til behandling af patienter med defekt mismatch repair system eller høj mikrosatellitinstabilitet tyk- og endetarmskræft

Bristol Myers Squibb (BMS) imødeser Medicinrådets anbefaling vedr. nivolumab + ipilimumab (herefter nivo+ipi) til behandling af patienter med defekt mismatch repair system eller høj mikrosatellitinstabilitet tyk- og endetarmskræft planlagt til 24. september 2025.

Indledningsvis vil BMS gerne anerkende det store arbejde, som sekretariatet har lagt i behandlingen af denne sag vedrørende den sundhedsøkonomiske model og takke for et godt samarbejde. BMS finder det dog beklageligt, at sagsbehandlingen har taget 8 måneder og dermed forsinket patienternes adgang. Flere gange i processen, har BMS lagt op til et dialogmøde, for at forklare rationalet bag den komplekse sundhedsøkonomiske model. Et dialogmøde tidligt i processen kunne potentielt have forkortet sagsbehandlingen og BMS vil derfor opfordre sekretariatet til at imødekomme dialogmøder tidligere i processen, så eventuelle udfordringer kan adresseres rettidigt og sagsbehandlingen kan fremmes til gavn for patienterne.

BMS er enige i, at det er en kompleks sundhedsøkonomisk model. Tilgangen for BMS' sundhedsøkonomiske model blev valgt på baggrund af tidligere mCRC-indsendelser til NICE i England, herunder pembrolizumab til behandling af patienter med ubehandlet MSI-H mCRC. Anvendelsen af en semi-Markov-model er mere hensigtsmæssig, når OS-data er umodne, og når eksterne data anvendes til at informere overlevelse efter progression. I indsendelsen for pembrolizumab blev brugen af en semi-Markov-model vurderet som passende for at kunne inkludere alle relevante helbredstilstande og klinisk plausible overgange mellem helbredstilstande. Derfor blev en semi-Markov-modelstruktur også valgt til indsendelsen for nivo+ipi til Medicinrådet i Danmark. Dette for at sikre hurtig adgang for patienter med MSI-H mCRC og ikke afvente OS data og dermed forsinke adgangen yderligere.

På trods af modellens kompleksitet er resultaterne fra base case-analysen robuste og konservative og scenarieanalyserne bekræfter robustheden af nivo+ipi som en omkostningseffektiv behandlingsmulighed. Yderligere er ovennævnte tilgang også blevet anvendt i Norge, hvor Nye Metoder d. 25.08.2025 har givet en positiv vurdering af nivo+ipi i kombination som førstelinjebehandling af patienter med defekt mismatch repair system eller høj mikrosatellitinstabilitet tyk- og endetarmskræft.

BMS imødeser Medicinrådets beslutning den 24. september, og ser frem til at patienter MSI-H vil få muligheden for at modtage denne behandling.

Med venlig hilsen,

Nicolai Fik
Market Access Direktør
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29.08.2025

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.09.2025
Leverandør	Bristol Myers-Squibb
Lægemiddel	Opdivo (nivolumab) i kombination med Yervoy (ipilimumab)
Ansøgt indikation	Behandling af patienter med defekt mismatch repair system eller høj mikrosatellitinstabilitet (dMMR/MSI-H) tyk- og endetarmskræft i 1. linje
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende priser på hhv. Opdivo (nivolumab) og Yervoy (ipilimumab):

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Forhandlet rabat ift. AIP
Opdivo	40 mg/4ml	3.359,21	[redacted]	[redacted]
Opdivo	100 mg/10 ml	8.344,80	[redacted]	[redacted]
Opdivo	120 mg/12 ml	10.013,77	[redacted]	[redacted]
Opdivo	240 mg/24 ml	20.027,53	[redacted]	[redacted]
Yervoy	5 mg/ml, 10 ml	23.349,52	[redacted]	[redacted]
Yervoy	5 mg/ml, 40 ml	93.190,02	[redacted]	[redacted]

Aftaleforhold

Amgros har prisaftaler på Opdivo og Yervoy, da de indgår i udbuddet for immunterapi.

Der er igangsat en prisregulering af immunterapier: Imfinzi (durvalumab), Opdivo (nivolumab), Tecentriq (atezolizumab), Keytruda (pembrolizumab), Libtayo (cemiplimab), Jemperli (dostalimab) og Bavencio (avelumab). Samtidig er der igangsat et udbud på de nye immunterapier: Hetronifly (serplulimab) og Tevimbra (tislelizumab).

De nye priser for alle immunterapier vil træde i kraft den [redacted].

I løbet af foråret 2025 har der været pipelinemøder med alle leverandører, som har immunterapi på markedet for at få overblik over de mange indikationer og deres ansøgninger til Medicinrådet. På basis af de indsamlede informationer er igangsættelsen af prisreguleringen i efteråret 2025 det optimale tidspunkt. På denne måde er det muligt at få så mange af de nye indikationer og immunterapier med og samtidig sikre at prisreguleringen ikke sker for hyppigt.

Konkurrencesituationen

Denne patientpopulation modtager i dag Keytruda (pembrolizumab) monoterapi.
Tabel 2 viser lægemiddeludgiften for Opdivo + Yervoy i relation til Keytruda for et års behandling.
Lægemiddeludgiften er beregnet på baggrund af en gennemsnitsvægt på 70,5 kg baseret på gennemsnitsvægten i studiet Checkmate-8HW.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Opdivo	40 mg/4 ml, 1 stk.	Opstart: 3 mg/kg* (i.v.) hver 3. uge i 4 serier Vedligehold: 6 mg/kg* (i.v.) hver 4. uge	[redacted]	[redacted]
Yervoy	5 mg/ml, 10 ml	1 mg/kg* (i.v.) hver 3. uge i 4 serier	[redacted]	[redacted]
Total pris for kombinationsbehandling med Opdivo + Yervoy				[redacted]
Keytruda	25 mg/ml, 4 ml	4 mg/kg*(i.v.) hver 6. uge	[redacted]	[redacted]

*Patientvægt 70,5 kg

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of nivolumab + ipilimumab for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC)

Contact information

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Table of contents

Tables and Figures

Abbreviations

Abbreviation	Definition	Abbreviation	Definition
1L	first line	KN	KEYNOTE
AE	adverse event	KRAS	Kirsten rat sarcoma virus
AIC	Akaike information criteria	LS	least squares
AJCC	American Joint Committee on Cancer	LSM	least squares mean
ATC	Anatomical Therapeutic Chemical Classification System	MAIC	matching indirect treatment comparison
BIC	Bayesian information criteria	mCRC	metastatic colorectal cancer
BICR	blinded independent central review	MDT	multidisciplinary team
BMS	Bristol Myers Squibb	mFOLFOX6	modified 5-fluorouracil + leucovorin + oxaliplatin
BRAF	B-Raf proto-oncogene	MID	minimally important difference
CDA-AMC	Canada's Drug Agency	MMR	mismatch repair
chemo	chemotherapy	MMRM	mixed model repeated measures
CI	confidence interval	MRI	magnetic resonance imaging
cLDA	constrained longitudinal data analysis	MSI	microsatellite instability
CM	CheckMate	MSI-H	microsatellite instability-high
CRC	colorectal cancer	N/A	not applicable
CSR	clinical study report	NA	not available

Abbreviation	Definition	Abbreviation	Definition
CT	computed tomography	NCT	National Clinical Trial
CTC	Common Toxicity Criteria	NICE	National Institute for Health and Care Excellence
CTCAE	Common Terminology Criteria for Adverse Events	NIVO	nivolumab
CTLA-4	cytotoxic T-lymphocyte antigen 4	NR	not reported
DBL	database lock	NTRK	neurotrophic tyrosine receptor kinase
DKK	Danish kroner	OESI	other event of special interest
DMC	Danish Medicines Council	ORR	overall response rate
dMMR	mismatch repair deficient	OS	overall survival
DRG	diagnosis-related group	PCR	polymerase chain reaction
DSU	Decision Support Unit	PD	Progressed Disease (health state)
ECOG	Eastern Cooperative Oncology Group	PD-1	programmed cell death protein 1
EMA	European Medicines Agency	PD-L1	programmed death-ligand 1
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core)	PD-L2	programmed death-ligand 2
ERG	Evidence Review Group	PEMBRO	pembrolizumab
ESS	effective sample size	PF	Progression Free (health state)
FA	final analysis	PFS	progression-free survival
FOLFIRI	5-fluorouracil + leucovorin + irinotecan	PHA	proportional-hazards assumption
FOLFOX	5-fluorouracil + leucovorin + oxaliplatin	PPS	postprogression survival
GHS	Global Health Status	PRO	patient-reported outcome
HR	hazard ratio	PS	performance status

Abbreviation	Definition	Abbreviation	Definition
HRQoL	health-related quality of life	QALY	quality-adjusted life-year
HSUV	health-state utility value	QoL	quality of life
HTA	health technology assessment	QxW	every x weeks
IA	interim analysis	RECIST	Response Evaluation Criteria in Solid Tumours
ICER	incremental cost-effectiveness ratio	RFA	radiofrequency ablation
ICH	International Council for Harmo-nisation	RKKP	Regionernes Kliniske Kvalitetsu-dviklingsprogram
IgG1	immunoglobulin G1	SAE	serious adverse event
IHC	immunohistochemistry	SLR	systematic literature review
IMAE	immune-mediated adverse event	SmPC	summary of product characteris-tics
IO	immuno-oncology	SOC	standard of care
IPD	individual patient data	TEM	treatment effect modifier
IPI	ipilimumab	TNM	tumour, node, metastasis
ITC	indirect treatment comparison	TSD	Technical Support Document
ITT	intention to treat	TTP	time to progression
IV	intravenous	UK	United Kingdom
JNHB	Joint Nordic assessment	US	United States
KM	Kaplan-Meier	VAS	visual analogue scale

1 Regulatory information on the medicine

Overview of the medicine	
Proprietary name	OPDIVO® + YERVOY®

Overview of the medicine	
Generic name	Nivolumab + ipilimumab
Therapeutic indication as defined by EMA	OPDIVO in combination with YERVOY for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC)
Marketing authorization holder in Denmark	Bristol Myers Squibb, Hummeltoftevej 49, 2830 Virum, Denmark
ATC code	L01XC17 and L01XC11
Combination therapy and/or co-medication	NIVO in combination with IPI
(Expected) Date of EC approval	19 December 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Presented in Appendix K
Other indications that have been evaluated by the DMC (yes/no)	Yes
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes. Is the product suitable for a joint Nordic assessment? No. If no, why not? Full HTA and cost-utility analysis will not be needed in Sweden and Finland.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Each millilitre of concentrate for solution for infusion contains 10 mg of NIVO. One vial of 4 mL contains 40 mg of NIVO. One vial of 10 mL contains 100 mg of NIVO. One vial of 12 mL contains 120 mg of NIVO. One vial of 24 mL contains 240 mg of nivolumab.[1] One vial of 24 mL contains 240 mg of NIVO.[1]

Overview of the medicine	
	Each millilitre of concentrate contains 5 mg IPI. One 10 mL vial contains 50 mg of IPI. One 40 mL vial contains 200 mg of IPI.[2]

2 Summary table

Summary	
Indication relevant for the assessment	Equivalent to the expected EMA indication: NIVO in combination with IPI for the treatment of adult patients with dMMR/MSI-H mCRC.
Dosage regiment and administration	Nivolumab 240 mg administered intravenously over 30 minutes + IPI 1 mg/kg every 3 weeks for 4 doses, followed by NIVO monotherapy 480 mg administered intravenously over 60 minutes every 4 weeks. In Danish clinical practice, NIVO dosing is expected to be based on weight of the patient.
Choice of comparator	The comparator is PEMBRO monotherapy for dMMR/MSI-H mCRC. PEMBRO is administered intravenously as 200 mg over 30 minutes every 3 weeks. PEMBRO was recommended as SOC in the same patient group by the DMC in September 2021 and represents the current SOC in dMMR/MSI-H mCRC. This is also reflected in the national Danish treatment guidelines.[3] In Danish clinical practice, PEMBRO dosing is based on weight of the patient.
Prognosis with current treatment (comparator)	CRC is one of the most common cancers in Denmark. Prevalence increases with age, and most cases present after 60 years of age.[3] In 2021, 3,953[4] people were diagnosed with CRC in Denmark; most of these diagnoses were colon cancer. Approximately 20% of CRC is stage IV (i.e., 859 people per year) at the time of diagnosis.[3] In addition, among people with stage II-III CRC, 20% are expected to relapse and develop stage IV CRC (i.e., 349 people per year).[5,6] The 5-year survival rate for people with rectum cancer in Denmark is 66% for men and 69% for women compared with 63% and 65% for colon cancer.[7] In Denmark, MMR status is a reflex test in all people with newly diagnosed CRC. Across all stages (I-IV), 15% of people are dMMR/MSI-H; for stage IV, it is 4%-7%. Prognosis depends on stage and/or tumour gene variants.[3] People with dMMR/MSI-H mCRC treated with chemotherapy have poorer outcomes than people with microsatellite stable/mismatch repair proficient mCRC. To date, no prospective phase 3 studies have reported results for anti–PD-1 compared directly with anti–PD-1 + anti–CTLA-4 therapies in dMMR/MSI-H mCRC. Median OS in patients with dMMR/MSI-H mCRC who received first-line systemic non-immunotherapy treatment has been reported to be 12.8 months.[7,8] Currently, there are no available real-world data on patients with dMMR/MSI-H mCRC who received PD-

Summary	
	1 monotherapy, but in the KN-177 study, the median OS was 77.5 months for PEMBRO at 5 years of follow-up.[9]
Type of evidence for the clinical evaluation	Indirect treatment comparison versus PEMBRO, the relevant comparator.
Most important efficacy endpoints (Difference/gain compared to comparator)	▪ PFS: [redacted] ▪ PFS: median months (95% CI) [redacted] NIVO+IPI: [redacted] – PEMBRO: 16.5 months (5.4-38.1)
Most important SAEs for the intervention and comparator	[redacted][10] Data on SAEs have not been identified for KN-177. The most common grade 3-5 adverse reactions in patients treated with PEMBRO in KN-177 were hypertension (7.2%), diarrhoea (5.9%), abdominal pain (5.2%), anaemia (5.2%) and hyponatraemia (5.2%).[50]
Impact on health-related quality of life	Clinical documentation: EORTC QLQ-C30 and EQ-5D-3L in CM 8HW (treatment difference at week 21) and KN-177 (treatment difference at week 18). **Treatment difference, LSM (95% CI)** **NIVO+IPI vs. chemo** / **PEMBRO vs. chemo** EORTC QLQ-C30: [redacted] / [redacted] EQ-5D-3L VAS: [redacted] / [redacted] EQ-5D-3L utility index: [redacted] / [redacted] ITCs between NIVO+IPI and PEMBRO are not available. Health economic model: Overall utility values per health state were used for the model because health-state occupation rather than treatment was seen as the most important factor determining utility. Utility decrements from AEs were modelled separately.
Type of economic analysis that is submitted	Cost-utility analysis using a semi-Markov model
Data sources used to model the clinical effects	▪ NIVO+IPI: CM 8HW for PF-to-PD transition; background mortality for PF-to-Death transition; CM 142 for PD-to-Death transition ▪ PEMBRO: Aggregate data from KN-177 and IPD from CM 8HW for PF-to-PD transition; background mortality for PF-to-Death transition; CM 142 for PD-to-Death transition (assumed that postprogression survival between NIVO+IPI and PEMBRO is equal)

Summary					
Data sources used to model the health-related quality of life	EQ-5D-3L collected in CM 8HW was mapped to EQ-5D-5L and was applied for the Danish utility index values.				
Life-years gained	▪ NIVO+IPI: [redacted] ▪ PEMBRO: 8.02 years				
QALYs gained	▪ NIVO+IPI: [redacted] ▪ PEMBRO: 6.38 QALYs				
Incremental costs	DKK 323,843.51				
ICER (DKK/QALY)	[redacted]				
Uncertainty associated with the ICER estimate	The extrapolations for PFS and OS involve some uncertainty; however, their impact on the ICER is minimal, resulting in a stable ICER.				
Number of eligible patients in Denmark	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
	90	90	90	90	90
Budget impact (in year 5)	[redacted]				

3 The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Colorectal cancer (CRC) includes tumours that develop in the large intestine (colon) or the rectum (end of the colon). CRC is the third most common cancer type and the second leading cause of cancer death worldwide.[11] Approximately 20% to 25% of people with CRC present with metastasis at diagnosis, and approximately 50% of people with non-metastatic CRC will eventually develop metastases.[12,13] Metastatic CRC (mCRC) is largely incurable; in the era before the introduction of pembrolizumab (PEMBRO), 5-year overall survival (OS) was less than 15%.[14,15] Since then, with the introduction of immunotherapies, the OS of patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) mCRC has improved significantly.

Many people with CRC are not diagnosed until their tumours are advanced[16]; this is partially because many symptoms of CRC are non-specific and common in adults without cancer. Symptoms include changes in bowel movements such as diarrhoea or constipation, altered stool consistency, feeling that the bowel has not emptied completely after a bowel movement, abdominal or rectal pain, and rectal bleeding or blood in the stool;

unexplained weight loss; unexplained iron-deficiency anaemia; fatigue; nausea; and vomiting.[17,18] Several demographic, behavioural, and environmental factors increase the risk of developing CRC. These include being overweight or obese, having a family history of CRC, having inflammatory bowel disease, smoking tobacco, and consuming red meat.[19] CRC is diagnosed at a relatively young age (50 years) compared with other cancer types such as lung cancer, leukaemia, pancreatic cancer, and liver cancer (60 years).

Biomarkers are defined as biomolecules, such as DNA, RNA, or proteins, produced by a person's body or tumour that may help in developing targeted treatments. Several biomarkers have been identified in CRC that are used to determine the choice of first- and second-line therapies.[20,21] The dMMR/MSI-H subtype of CRC arises from germline or sporadic impairments of the mismatch repair (MMR) system, the protein complex responsible for correcting errors during DNA replication.[22] Deficient MMR causes DNA sequence mismatches to occur more frequently, particularly in the short repetitive regions of DNA called *microsatellites*, which become more prone to pathogenic variants and differences in length. This condition, known as MSI, is potentially oncogenic when it occurs in coding regions of genes with a role in carcinogenesis.[23] Overall, dMMR/MSI-H accounts for 15% of CRC cases; however, the prevalence of MSI differs across disease stages for CRC and can range from approximately 15% in stages II-III to approximately 5% to 7% in stage IV.[22,24,25]

Tumour stage is associated with survival.[22] The 5-year survival rate among people in Denmark with rectum cancer is 66% for men and 69% for women compared with 63% and 65% for colon cancer.[7] However, the 5-year survival rate significantly decreases for people with CRC in advanced stage.[26] The MSI-H phenotype confers distinct clinical/pathological features and recurrence patterns for CRC tumours and is associated with more frequent local recurrence and peritoneal metastases than microsatellite stable tumours.[27]

Median OS in patients with dMMR/MSI-H mCRC who receive first-line systemic non-immunotherapy treatment was reported to be 12.8 months.[7,8] Currently, there are no available real-world data on patients with dMMR/MSI-H mCRC who receive programmed cell death protein 1 (PD-1) monotherapy, but in KEYNOTE-177 (KN-177), the median OS was 77.5 months for PEMBRO at 5 years of follow-up.[9] CRC has a negative effect on health-related quality of life (HRQoL), and traditional treatments have a high rate of adverse events (AEs), which can worsen HRQoL.[28] Treatment with chemotherapy in patients with dMMR/MSI-H mCRC leads to a decline in HRQoL including a worsening in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core) (EORTC QLQ-C30) Global Health Status (GHS) and functional scale scores from baseline to 18 weeks, whereas treatment with immuno-oncology (IO) agents results in improved HRQoL.[29]

3.2 Patient population

In Denmark, CRC is one of the most common cancer types. The prevalence increases by age, and most cases present after 60 years of age.[3] The median age at diagnosis for CRC has been reported to be 66 years for men and 69 years for women.[16] In 2021, the

prevalence of CRC in Denmark was estimated to be 42,194,[30] and 3,953 people were newly diagnosed with CRC (of whom most had colon cancer).[4] There are limited epidemiological data for dMMR/MSI-H mCRC in Denmark; therefore, Table 1 presents the incidence and prevalence in Denmark for CRC based on data from 2021, assumed at a flat rate due to lack of data.

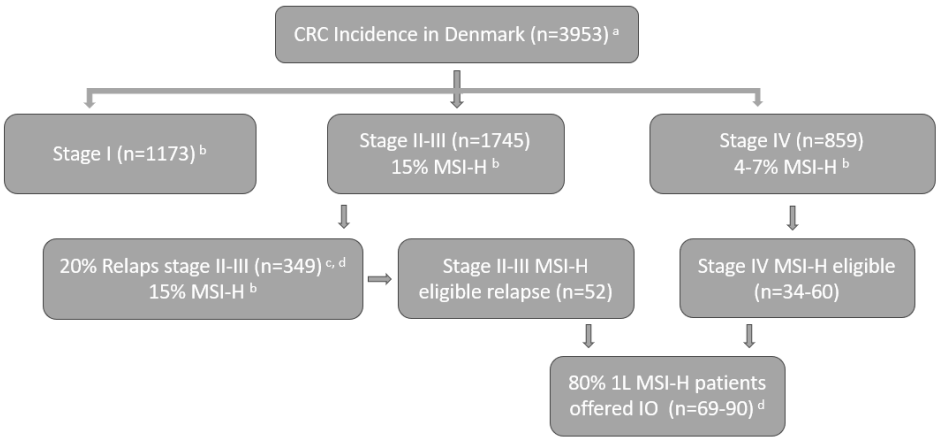
Table 1. Incidence and prevalence of CRC in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	3,953	3,953	3,953	3,953	3,953
Prevalence in Denmark	42,194	42,194	42,194	42,194	42,194

Sources: DCCG (2023)[4,30]

Figure 1 shows the patient calculation for dMMR/MSI-H mCRC in Denmark, starting with an assumed CRC incidence of 3,953.[4] Approximately 20% of CRC is stage IV (i.e., 859 people per year) at the time of diagnosis.[3] In addition, among people with stage II-III CRC, 20% are expected to relapse and develop stage IV CRC (i.e., 349 people per year).[5,6] In Denmark, testing for MMR status is recommended in all individuals newly diagnosed with CRC. Across all stages (I-IV), 15% of people are dMMR/MSI-H; for stage IV, 4%-7% are dMMR/MSI-H.[3] It is estimated that 80% of eligible patients will be offered IO treatment. Therefore, overall, up to approximately 90 patients per year will be eligible for nivolumab + ipilimumab (NIVO+IPI) (Figure 1; Table 2).

Figure 1. Patient calculation for dMMR/MSI-H mCRC eligibility for first-line treatment in Denmark



Note: 176 patients of the 3953 did not have staging evaluated.

Sources: [a] DCCG (2023)[4]; [b] Gelsomino et al. (2016)[22]; [c] Houlind Petersen (2023)[5]; [d] DCCG (2018)[31]

Table 2. Estimated number of patients eligible for treatment

Year	2025	2026	2027	2028	2029
Number of patients in Denmark who are eligible for treatment in the coming years	90	90	90	90	90

Sources: DCCG (2023)[4]; DCCG (2023)[3]; Houlind Petersen (2023)[5]; Nors et al. (2023)[6]; Gelsomino et al. (2016)[22]; DCCG (2018)[31]

3.3 Current treatment options

In Denmark, the Danish Multidisciplinary Cancer Group (Danske Multidisciplinære Cancer Grupper) and Regionernes Kliniske Kvalitetsudviklingsprogram (RKKP) have provided national guidelines for the treatment of mCRC.[3] Table 3 presents the key recommendations for individuals with mCRC relevant to this appraisal. Patients with dMMR/MSI-H mCRC should be offered first-line treatment with PEMBRO.[3,7]

Table 3. Key recommendations for the treatment of mCRC in Denmark

Vigtigste anbefalinger	Key recommendations	Level of evidence[a]
Alle patienter, med nydiagnosticeret metastatisk kolorektal cancer (mKRC) eller recidiv efter tidligere kurativ behandlet mKRC, skal vurderes ved relevant MDT med henblik på at fastlægge behandlingsstrategi og behandlingsmål (kurativt/potentielt, kurativt eller palliativt)	All patients with newly diagnosed mCRC or recurrence after previously curatively treated mCRC should be assessed by appropriate MDT to determine treatment strategy and treatment goals (curative/potential, curative or palliative)	A
Ved valg af den endelige behandlingsstrategi skal følgende faktorer vurderes: udbredning af sygdom (oligometastatisk vs. udbredt metastatisk), lokalisation af primær tumor, hvorvidt primær tumor er in situ, den tumorbiologiske profil med oplysninger om RAS og BRAF-mutations status, MMR-status, komorbiditet, almen tilstand samt patient præferencer	When choosing the final treatment strategy, the following factors should be assessed: disease distribution (oligometastatic vs. metastatic), location of primary tumour, whether primary tumour is in situ, tumour biological profile with information on *RAS* and *BRAF* variant status, MMR status, comorbidity, general condition and patient preferences	A
Første linje behandling hos patienter med mKRC og god almen tilstand/performance status	**First-line treatment in patients with mCRC and good general status/performance status**	
Patienter bør tilbydes systemisk onkologisk behandling, hvor behandlingsvalget afhænger af lokalisation af primærtumor, den tumorbiologiske profil med oplysninger om RAS og BRAF-mutations status, MMR-status, komorbiditet, almen	Patients should be offered systemic oncological treatment, where the choice of treatment depends on the location of the primary tumour, the tumour biological profile with information on *RAS* and *BRAF* variant status, MMR status, comorbidity,	A

Vigtigste anbefalinger	Key recommendations	Level of evidence[a]
tilstand, evt. Tidligere adjuverende behandling samt patient præferencer	general condition, any previous adjuvant therapy and patient preferences	
Patienter med dMMR mKRC bør tilbydes behandling med pembrolizumab	Patients with dMMR mCRC should be offered treatment with pembrolizumab	A
Behandling efter første linje behandling	**Treatment after first-line treatment**	
Behandlingen af patienter med mKRC opfattes som et 'continuum of care' og patienter med mKRC bør eksponeres for alle tilgængelige aktive stoffer I deres behandlingsforløb	The treatment of patients with mCRC is perceived as a 'continuum of care' and patients with mCRC should be exposed to all available active substances during their course of treatment	A

Source: DCCG (2023)[3]

The prognosis in patients is dependent on stage and/or tumour gene variant.[3] Patients with dMMR/MSI-H mCRC treated with chemotherapy have poorer outcomes than patients with mismatch repair proficient or microsatellite stable mCRC. To date, no prospective phase 3 studies have reported results for anti−PD-1 compared directly to anti−PD-1 + anti−cytotoxic T-lymphocyte antigen 4 (CTLA-4) therapies in dMMR/MSI-H mCRC.[3] In patients with dMMR/MSI-H mCRC who undergo first-line systemic treatment, OS has been reported to be 12.8 months.[7,8] Currently, there are no available real-world data on patients with dMMR/MSI-H mCRC who received PD-1 monotherapy, but in KN-177, the median OS was 77.5 months for PEMBRO at 5 years of follow-up.[9]

3.4 The intervention

NIVO is a human, monoclonal immunoglobulin G4 antibody that acts as a PD-1 inhibitor, blocking the interaction of PD-1 with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2).[32,33] NIVO binds with high affinity to PD-1 receptors on T cells and selectively disrupts inhibitory signalling triggered by PD-L1 and PD-L2, thereby restoring normal T-cell antitumour immune response.[32] IPI is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86.[34] Blockade of CTLA-4 enhances T-cell activation and proliferation, including that of tumour-infiltrating T-effector cells. Inhibition of CTLA-4 signalling can also reduce T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including the antitumour immune response.[35] NIVO+IPI mediates inhibition, which results in enhanced T-cell function and improved antitumour responses in mCRC. Table 4 summarises the use of NIVO with IPI in this indication.

Table 4. Description of NIVO+IPI

Overview of intervention	
Indication relevant for the assessment	NIVO in combination with IPI is indicated for the first-line treatment of adult patients with dMMR/MSI-H mCRC

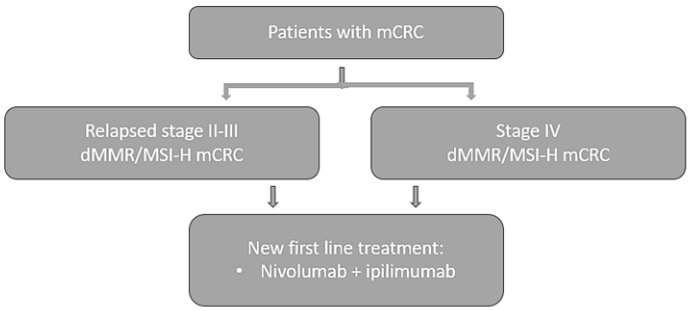
Overview of intervention	
ATMP	N/A
Method of administration	Intravenous infusion
Dosing	240 mg NIVO with 1 mg/kg IPI every 3 weeks for 4 doses, then 480 mg NIVO every 4 weeks. In Danish clinical practice, NIVO dosing is expected to be based on the weight of the patient.
Dosing in the health economic model (including relative dose intensity)	▪ NIVO: 3 mg/kg every 3 weeks the first 4 times when combined with IPI, then 6 mg/kg every 4 weeks. ▪ IPI: 1 mg/kg every 3 weeks up till 4 times. ▪ Relative dose intensity: 100% for all treatments.
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment with NIVO should be continued if clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to a maximum of 2 years, per the SmPC). Treatment with IPI is for a maximum of four doses.
Necessary monitoring, both during administration and during the treatment period	Patients should be monitored for cardiac and pulmonary adverse reactions continuously (at least up to 5 months after the last dose), as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. NIVO+IPI should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.
Need for diagnostics or other tests (e.g., companion diagnostics). How are these included in the model?	MMR status is a reflex test in all patients with newly diagnosed CRC in Denmark.
Package size(s)	Each millilitre of concentrate for solution for infusion contains 10 mg of NIVO. One vial of 4 mL contains 40 mg of NIVO. One vial of 10 mL contains 100 mg of NIVO. One vial of 12 mL contains 120 mg of NIVO. One vial of 24 mL contains 240 mg of NIVO. Each millilitre of concentrate contains 5 mg IPI. One 10 mL vial contains 50 mg of IPI. One 40 mL vial contains 200 mg of IPI.

Sources: YERVOY SmPC (2024)[2]; OPDIVO SmPC (2024)[1]

3.4.1 The intervention in relation to Danish clinical practice

NIVO+IPI is positioned as first-line treatment of adult patients with dMMR/MSI-H mCRC and will replace PEMBRO in this setting. Figure 2 presents the proposed position of NIVO+IPI in the treatment pathway.

Figure 2. Position of NIVO+IPI in the treatment pathway



Sources: DCCG (2023)[3]; OPDIVO SmPC (2024)[1]

3.5 Choice of comparator(s)

In Denmark, the first-line comparator treatment for patients with dMMR/MSI-H mCRC is PEMBRO (Table 5). Although some patients with mCRC may receive chemotherapy, according to treatment guidelines, PEMBRO is standard of care (SOC) for those eligible to receive IO therapy and therefore is the only relevant comparator in Denmark.

Table 5. Description of PEMBRO

Overview of comparator	
Generic name	Pembrolizumab
ATC code	L01XC18
Mechanism of action	PEMBRO (Keytruda, Merck) is a humanised monoclonal IgG1 antibody that binds to PD-1 blocking its interactions with the PD-1 and -2 ligands and releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumour immune response.
Method of administration	Intravenous infusion
Dosing	PEMBRO 200 mg intravenously every 3 weeks for up to 35 cycles. In Danish clinical practice, PEMBRO dosing is based on the weight of the patient.
Dosing in the health economic model (including relative dose intensity)	▪ PEMBRO: 6 mg/kg every 6 weeks ▪ Relative dose intensity: 100%
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity (and up to a maximum duration of 2 years, as per clinical practice in Denmark)

Overview of comparator	
Need for diagnostics or other tests (i.e., companion diagnostics)	No. MMR status is a reflex test in all patients with newly diagnosed CRC in Denmark.
Package size(s)	One 4-mL vial contains 100 mg PEMBRO

Source: Keytruda SmPC (2024)[36]

3.6 Cost-effectiveness of the comparator

PEMBRO is recommended by the DMC for first-line treatment of patients with dMMR/MSI-H mCRC.[7,37]

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 6 presents the relevant efficacy outcomes necessary to evaluate the effect of NIVO+IPI compared with SOC in Denmark.

Table 6. Efficacy outcome measures relevant for the application

Outcome measure	Timepoint[a]	Definition	How was the measure investigated/method of data collection
PFS From CM 8HW, BMS data on file (2024)[10]; BMS data on file (2023)[38]	Median follow-up: [redacted] months at the interim analysis[10]	PFS by BICR was defined as the time from randomisation to the date of documentation of disease progression or death from any cause, whichever occurred first.[38]	Contrast-enhanced CT of the chest and CT/MRI of the abdomen, pelvis, and all other known/suspected sites of disease were performed. Tumour assessment occurred every 6 weeks (± 7 days) from randomisation for the first 24 weeks and every 8 weeks (± 7 days) thereafter until BICR-confirmed progression and treatment discontinuation (including treatment beyond progression), whichever occurred later. BICR reviewed all scans and remained blinded to treatment arm and investigator assessment.[10]
PFS From KN-177, [39]	Median follow-up: 32.4 months at the second interim analysis [39]	PFS was defined as the time form randomisation to first disease progression, as assessed by central review according to RECIST (version 1.1),	Disease progression was verified by imaging, performed at a central location. [39]

Outcome measure	Timepoint[a]	Definition	How was the measure investigated/method of data collection
		or death from any cause. [39]	

[a] Timepoint for data collection used in analysis (follow-up time for time-to-event measures).

Validity of outcomes

Table 7 presents the validity of efficacy endpoint measures relevant for the application. Progression-free survival (PFS) has been validated as a surrogate endpoint for OS in patients with MSI-H/dMMR mCRC receiving immunotherapy, using data from CheckMate 142 (CM 142). The patient-level correlation between PFS and OS was strong in all cohorts of the CM 142 study (Spearman's rho ranging between 0.83 and 0.92 depending on treatment) providing supportive evidence for the validation of PFS as a suitable surrogate endpoint for OS for patients with MSI-H/dMMR mCRC receiving immunotherapy.[40]

Table 7. Validity of efficacy endpoint measures relevant for this application

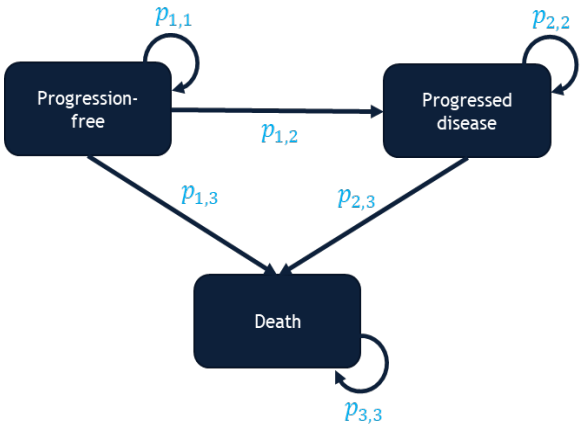
Endpoint measure and source	Validity
PFS BMS data on file (2024)[10]	The outcome of PFS by BICR is consistent with other studies exploring the use of other anticancer agents in this patient population. RECIST v1.1 criteria were used by investigators and BICR to assess tumour response and PFS.

4 Health economic analysis

4.1 Model structure

As with many other malignancies, the course of disease for patients with mCRC is characterised by a progression-free phase after receiving initial treatment. Hereafter, patients will either progress, die due to mCRC without a diagnosis of progression, or die due to unrelated causes. Once progressed, patients will either continue to receive treatment for progressive disease and eventually die due to natural causes or die due to mCRC. Although partitioned survival models are frequently used for economic evaluations in oncology, use of a semi-Markov model is more suitable when OS data are immature and when external data are used to inform time-to-event data such as post-progression survival. A three-state semi-Markov model was developed using data from CM 8HW, CM 142, and KN-177 to estimate the cost-effectiveness of NIVO+IPI versus PEMBRO. Figure 1 shows the generalised model framework including the transition pathways across the following health states: Progression Free (PF), Progressed Disease (PD), and Death.

Figure 3. Three-state semi-Markov model structure



The model uses a 28-day model cycle length. This cycle length allows for most treatment regimens to fit in a single model cycle while being sufficiently short enough to capture all relevant events of interest. In line with DMC guidelines, the model cycle length is half-cycle corrected. 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" (i.e., PFS cannot be higher than OS) and it allows increased flexibility on assumptions regarding postprogression survival (e.g., if the PD transition is time varying).

Thus, in this semi-Markov model, the transition probability from PD to Death and the probability of remaining in PD depend on the time spent in the PD state. For PFS, time-varying estimates can be easily 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 PD is considerably more complex.

Therefore, in the model, such time-dependent probabilities have been implemented in a VBA macro for efficiency purposes. Transition probabilities are estimated in a separate Excel sheet for all transitions for all states for each treatment that are then loaded into the macro. In the macro, the health-state occupancy is then calculated using a three-dimensional array in which 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 PF, the time spent in the health state is equal to the model cycle length; therefore, including the sojourn time does not make a difference. However, for PD, 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*.

Within the model, patients transition through the health states according to a set of transition probabilities. Transitions from PF to PD ($p_{1,2}$) are estimated using individual patient data (IPD) from the clinical trial CM 8HW for NIVO+IPI and through a matching

indirect treatment comparison (MAIC) using IPD from CM 8HW and aggregate data from KN-177 for PEMBRO. For the transitions from PF to Death ($p_{1,3}$), background mortality is used for both treatments. Individual patient data from CM 142 for the NIVO+IPI arm is used to estimate the transitions from PD to Death ($p_{2,3}$); these transitions are assumed equal for both treatments. Further details on the model structure and the underlying data are presented in the section below. Sections 7 and 8 present more details on the clinical data used, the rationale and assumptions behind the choices of data, and the estimation and choice of transition probabilities in the model.

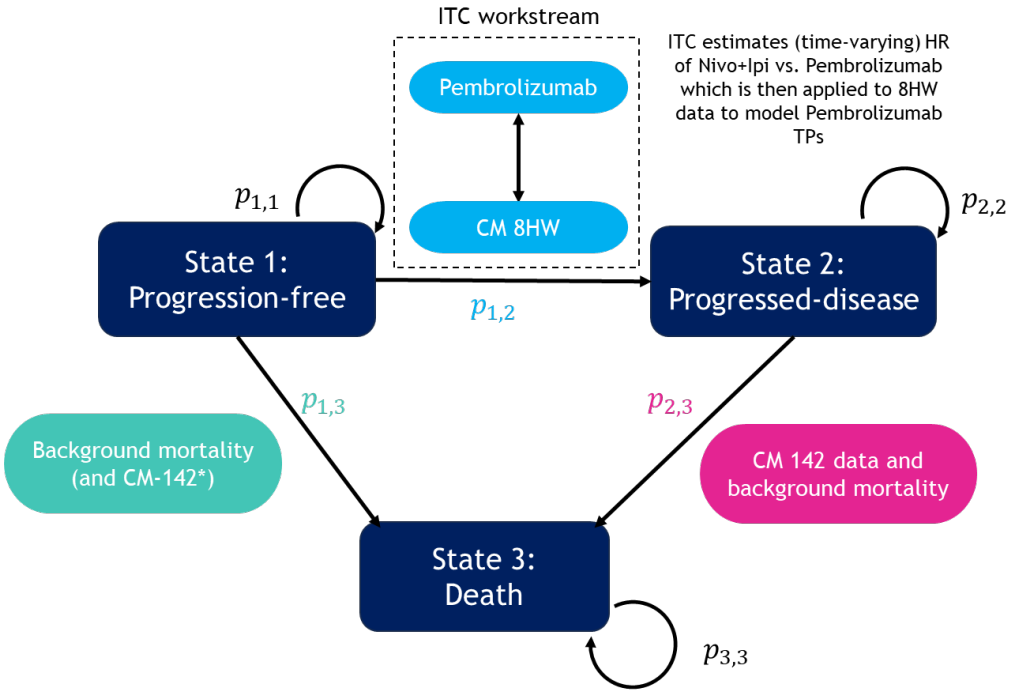
Summary and background cost-effectiveness model and indirect treatment comparison

Rationale for using a semi-Markov modelling approach

To guide the modeling process, two cost-effectiveness technology appraisals (TAs); TA709 (Pembro in patients with untreated MSI-H mCRC) and TA439 (multiple technology appraisal of cetuximab and panitumumab with chemotherapy in patients with untreated mCRC) were identified. Both NICE submissions incorporated a semi-Markov model structure. Use of a semi-Markov model is more suitable when OS data is immature and when external data is used to inform TTE data such as post-progression survival.

The use of a semi-Markov approach was the preference of the 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). 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.

Model structure



Model structure

*The highest per cycle probability of estimates derived using CM-142 and background mortality was used in a scenario analysis to model PF-D

Health state transition probabilities – choice of data sources and assumptions

For estimations of TTP [p(1,2)], individual patient data (IPD) from CM-8HW were used to inform p(1,2) for the Nivo + Ipi arm. A MAIC was performed using aggregate data from KN-177 and IPD from CM-8HW, comparing Pembro with re-weighted Nivo + Ipi data. The estimated relative efficacy from the MAIC between Nivo + Ipi and Pembro was used to estimate p(1,2) for the Pembro arm.

Estimations of p(1,3) utilised background mortality data for all treatment arms in the base case scenario.

For estimations of post-progression survival [p(2,3)], CM-142 data was used in lieu of CM-8HW data as CM-8HW OS data was immature and unavailable at the time of analysis. Although the transition is based on CM-142 data, the hazard of death could never fall below background mortality. Thus, if a single transition to death for cycle x based on CM-142 was lower than background mortality, background mortality would be used.

An outline of the sources for each health state transition is presented in the table below.

Transition	Description	Data source

Progression-free to progressed disease (PF-PD, p1,2)	Time to progression (TTP), defined as time from model entry to progression	CM8HW for NIVO + IPI, PFS ITC for PEMBRO
Progression-free to death (PF-D, p1,3)	Pre-progression survival (PrePS), defined as time from model entry to deaths occurring before progression	General population mortality and CM142 data in scenario analysis due to lack of data from CM8HW
Progressed disease to death (PD-D, p2,3)	Post-progression survival (PPS), defined as time from progression to death	CM142 PPS data – assumed equal for all model arms in base case. Note, it was assumed that the hazard of death is never lower than background mortality

Overview of model structure and transitions

Transition probabilities for Nivo+Ipi (PF to PD, p 1,2)

For Nivo + Ipi, the transition from PF-PD was estimated by fitting parametric models to the TTP data from CM-8HW.

Among Nivo + Ipi patients, the median TTP (in months, please see Figure below) was not reached (95% CI 38.44 – NR), while among chemotherapy patients the median TTP was 7.39 months (95% CI 5.68 – 10.90). The calculated HRs between the two trial arms, under the proportional hazards (PH) assumption, was 0.34 (95% CI 0.23 – 0.51).

KM curve presenting the p(1,2) transition for the Nivo + Ipi and chemotherapy arms in CM-8HW

As the PH assumption did not hold, independent models were fit to the data. Based on AIC as well as the plausibility of extrapolation, for Nivo + Ipi the Generalized gamma model was chosen as the best option (please see Figure below).

Standard parametric fits of the p(1,2) transition for the CM-8HW Nivo + Ipi arm, extrapolated beyond the observed trial period

As no direct evidence is available comparing Pembro with Nivo + Ipi in MSI-H mCRC patients, a MAIC was performed comparing Pembro with Nivo + Ipi using aggregate data from KN-177 and IPD from CM-8HW. An unanchored MAIC was chosen as the base case.

Based on the model structure, the MAIC would ideally compare the TTP between Pembro and Nivo + Ipi. TTP includes only the disease-related progression, whereas PFS includes both disease-related progression and death. As mortality is included and accounted for in the transition PF to death and PD to death in the CEM, background mortality is adjusted for in the PFS input (attempted to be 'excluded' from PFS results from the ITC) in the estimation of parameters in R , to avoid double counting mortality in the CEM.

Transition probabilities for Pembro (PF to PD, p 1,2)

Although TTP would ideally be used for the comparison of nivo-ipi vs pembro, TTP data are unavailable for KN-177. For KN-177 only PFS data is published, i.e. including patients that progress as well as die. To enable a comparison of similar data across trials, the MAIC estimated the comparative efficacy for the outcome PFS of Nivo + Ipi vs. Pembro. The resulting time-varying HRs of the ITC include both disease-related progression as well as background mortality. However, as described in the paragraph above, the CEM only uses TTP (i.e. disease-related progression) for the PF to PD transition, without the

addition of modelled background mortality as this is already included in the PF-D transition.

Following the additive hazards/relative survival approach when modeling survival outcomes, it is possible to distinguish between disease-related events, i.e. progressions, and background mortality, when the expected population background mortality is defined (e.g. based on population life tables). For the CEM, this approach was used to align with the model structure and avoid double-counting of background mortality.

Therefore, background mortality was adjusted for and only the estimated disease-related component was used for the time-varying HRs in the CEM, which results in differences between the time-varying HRs estimated in the MAIC and those used in the CEM. The time-varying HR curve in the base case, adjusted for (attempted to 'exclude') background mortality used in the CEM, can be seen in the figure below. For more details around the background mortality in the ITC and the CEM, please see section Background mortality: ITC vs CEM below.

Notably, the HR based on the disease-related component alone remains relatively constant after the first year. This suggests that the hazards for disease-related events (progressions) are estimated to stay relatively constant between NIVO+IPI and Pembro after the first year.

Whereas there is an increasing HR over time of combined background and disease-related mortality in NIVO+IPI versus Pembro observed in the ITC, with the HR approaching 1. As many patients in the Pembro and especially Nivo + Ipi arm did not progress, these arms had a considerable amount of estimated background mortality. Over time, the HR considering disease-related events and background mortality approached 1, indicating while there is a lower hazard for NIVO+IPI compared to Pembro initially, disease related and background mortality hazards combined are similar at around ~10 years.

Time-varying HR estimated in the CEM solely not considering BGM

The alignment of the HRs from the MAIC and the HRs from the CEM can be demonstrated by comparing the curves from the ITC without background mortality and the curve from the CEM. Both curves align, as seen in the figure below.

HR estimated in the CEM (without background mortality) and MAIC.

The model assumed that the HR between treatments of PFS (adjusted for background mortality in time-varying HR analyses) was approximately comparable to the HR of TTP. The estimated comparative efficacy of Pembro vs. Nivo + Ipi is then applied to the Nivo + Ipi transition rate, to estimate the transition probability of Pembro.

To obtain the Pembro transition probabilities from PF to PD, the Nivo + Ipi transition probabilities were converted to a rate and multiplied with the time-varying HRs of Pembro vs Nivo + Ipi according to the following formula:

$$Transition\ rate\ Pem = \frac{-\ln(1 - per\ cycle\ Niv + ipi\ p)}{cycle\ length} * HR$$

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

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

Background mortality: ITC vs CEM

The difference between the time-varying HRs from the ITC and the CEM can be explained due to the ITC and graphic from R model PFS, a composite of disease-related events (progressions) and background mortality (BGM). However, it is possible to distinguish BGM within the estimation. As the transition of relevance for the CEM (PF to PD) should not include BGM events, the parameters applied in the CEM exclude BGM. Therefore, the progression parameters that feed into the model are identical with the only difference being that BGM (or rather BGM events) is adjusted for. Thus, the parameters exported for the CEM do *not* include BGM as this is modelled separately in the progression free to death transition

For the parametric modeling of progression-free survival (PFS) in the indirect treatment comparison (ITC), we estimated model parameters using an internal additive hazards/relative survival approach, aligned with NICE TSD 21 guidelines and Oostrum et al. (2021 [doi: 10.1016/j.jval.2021.03.008]). This method differentiates between disease-related events (progressions) and background mortality for PFS. The PFS models were fitted using the flexsurv package in R (https://cran.r-project.org/web/packages/flexsurv/vignettes/flexsurv.pdf), incorporating expected background mortality data from life tables into the model, which allowed for separate estimations of background mortality and disease-related events. The standard R output presents model parameters for disease-related events, with background mortality needing to be added for absolute PFS estimation. Background mortality data was sourced from UK Office of National Statistics (ONS) life tables (2018–2020).

4.2 Model features

The key model features are summarised in Table 8.

Table 8. Features of the economic model

Model features	Description	Justification
Patient population	Adults (aged 18 years and older) with dMMR/MSI-H mCRC	In line with the EMA label and anticipated use in Denmark
Perspective	Limited societal perspective	According to DMC guidelines
Analytical method	Semi-Markov model	Modelling technique commonly used in oncology when a partitioned survival model is not suitable.
Time horizon	Lifetime (40 years)	As the mean age of CM 8HW is 60.9 years, a 40-year time horizon was considered adequate to capture all health benefits and costs in line with DMC guidelines.

Model features	Description	Justification
Cycle length	28 days	Allows most treatment regimens to fit within a single model cycle while being short enough to capture all relevant events of interest.
Half-cycle correction	Yes	According to DMC guidelines
Discount rate	3.5%	The DMC applies a discount rate of 3.5% for all years.
Intervention	NIVO+IPI	See Section 3.4
Comparator(s)	PEMBRO	See Section 3.5
Outcomes	OS, PFS	In line with key health-state outcomes commonly used in economic evaluations for cancer, as well as the primary and key secondary endpoints of CM 8HW
Costs	▪ Treatment-related costs ▪ Subsequent treatment costs ▪ Resource use costs ▪ Patient time costs ▪ Transportation costs	Standard costs for patients with mCRC
Utilities	Overall health-state utilities derived from CM 8HW AE disutilities obtained from literature	Health-state utility values obtained from CM 8HW in which patients completed the EQ-5D-3L questionnaire. EQ-5D-3L mapping to EQ-5D-5L was applied for the Danish utility index values. Evidence on the disutilities associated with managing grade 3 or above AEs in patients with mCRC is lacking. Estimates for many disutilities were derived from studies in other cancer types.

5 Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) to identify relevant clinical evidence was conducted as described in Appendix H. This SLR identified the CM 8HW and KN-177 trials. The indication for NIVO+IPI included in this submission is based on the pivotal CM 8HW trial comparing NIVO+IPI versus NIVO monotherapy or chemotherapy. Most information on CM 8HW was taken from the clinical study report[10]; however, an article describing the study was published in November 2024 after this submission was developed.[41]

KN-177 is included because PEMBRO is the first-line comparator treatment for patients with dMMR/MSI-H mCRC in Denmark.

In addition, CM 142 is described because it provides supporting information. CM 142 was not identified in the clinical SLR due to its non-comparative nature but is included for completeness. The study details are described in Section 6.1.1.2 and in Appendix A, as it is used in the economic model. CM 8HW is an interventional follow-on study of CM 142, meaning further published results would be of particular interest in a future SLR. Moreover, CM 142 reported positive responses to NIVO+IPI regarding outcomes such as OS, PFS, and AEs. Table 9 summarises the relevant literature related to CM 8HW, CM 142, and KN-177.

Table 9. Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cutoff and expected data cutoffs)	Used in comparison of
▪ BMS data on file. Interim clinical study report for study CA2098HW. 2024.[10] ▪ Andre T, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): first results of the CheckMate 8HW study. J Clin Oncol. 2024;42(suppl 3):LBA768-LBA.[42] ▪ Lenz HZ, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Expanded efficacy analysis from CheckMate 8HW. J Clin Oncol. 2024;42(16_suppl):3503.[43]	CM 8HW	NCT04008030	Start: 5 August 2019 Completion: The study is ongoing Data cutoff: 12 October 2023 Database lock: 15 November 2023	NIVO+IPI vs. PEMBRO
▪ Shiu KK, et al. LBA32 Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomised phase III KEYNOTE-177 study. Ann Oncol. 2023;34:S1271-72.[9] — Presented at European Society for Medical Oncology (ESMO); 20-24 October 2023.[44] ▪ Diaz LA Jr, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2022 May;23(5):659-70.[45] ▪ Andre T, et al. Final overall survival for the phase III KN177 study: pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). J Clin Oncol. 2021;39(15_suppl):3500.[29] ▪ André T, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020 Dec 3;383(23):2207-18.[39]	KN-177	NCT02563002	Start: 30 November 2015 Completion: 17 July 2023	NIVO+IPI vs. PEMBRO

▪ Lenz H, et al. First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 64-month (mo) follow-up from CheckMate 142 J Clin Oncol. 2024;42(3_suppl):97.[46]	CM 142	NCT02060188	Start: 12 March 2014 Data cutoff: 15 September 2022 Completion: 22 October 2024	Supplementary information only.

5.2 Literature used for the assessment of health-related quality of life

Because QoL data were collected for the relevant health states in the model as part of CM 8HW, these were used in the economic model. These utility values were seen to reflect the utility for each health state regardless of treatment because utility, except for AEs, could primarily be seen to depend on disease state rather than treatment. See Section 10 for details on HRQoL.

Table 10. Relevant literature included for (documentation of) health-related quality of life (See Section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Authors. Article title. Journal. Year; volume(issue): pp [reference number]	E.g. First line metastatic recurrence	

5.3 Literature used for inputs for the health economic model

The economic model was developed based on previous health technology assessment (HTA) submissions with additional inputs from clinical trial information and previous DMC submissions (Table 11); no literature reviews were conducted.

Table 11. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Lenz H, et al. First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 64-month (mo) follow-up from CheckMate 142 J Clin Oncol. 2024;42(3_suppl):97.[46] Overman MJ, et al. Nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): five-year follow-up from CheckMate 142 J Clin Oncol. 2022;40(16_suppl):3510.[47] André T, et al. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Ann Oncol. 2022 Oct;33(10):1052-60.[48] Lenz HJ, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 study. J Clin Oncol. 2022 Jan 10;40(2):161-70.[49]	CM 142 trial data used for extrapolation of PD-to-Death transition	Clinical trial	Section 8.1.1.2
Medicinrådet. Medicinrådets anbefaling vedrørende pembrolizumab til behandling af MMR-deficient (MSI-H/dMMR) metastatisk kolorektalkræft. 21 September 2021. https://medicinraadet-classic.azureedge.net/media/mw3l1qf0/medicinr%C3%A5dets-anbefaling-vedr-pembrolizumab-til-mcrc-vers-1-0_adlegacy.pdf. Accessed 9 July 2024.[7]	Resource use per health state	DMC submission	Section 11.4; Table 56
	Percentage of patients receiving subsequent therapy		Section 11.6; Table 60
	Mean time on subsequent treatment (weeks)		Section 11.6; Table 59
	Hours per visit per cycle for patient costs		Section 11.7; Table 61
DMC. Appendix to the Medical Council's recommendation regarding pembrolizumab for the treatment of MMR-(MSI-H/dMMR) metastatic colorectal cancer. 2021.	Incidence of grade 3-4 AEs for PEMBRO	DMC submission	Section 9.1

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
https://medicinraadet-classic.azureedge.net/media/j2blfrey/bilag-til-medicinr%C3%A5dets-anbefaling-vedr-pembrolizumab-til-mcrc-vers-1-0_adlegacy.pdf. Accessed 23 August 2024.[37]			
Andre T, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020 Dec 3;383(23):2207-18.[39]	Incidence of grade 3-4 AEs for PEMBRO	KN-177 trial publication	Section 9.1
Freeman K, et al. Fluorouracil plasma monitoring: the My5-FU assay for guiding dose adjustment in patients receiving fluorouracil chemotherapy by continuous infusion. Coventry: Warwick Evidence, 2014.[50]	Disutility of grade 3-4 AEs (including hepatitis, neutropenia, diarrhoea/colitis, asthenia) Duration of grade 3-4 AEs (including hepatitis, neutropenia, rash, diarrhoea/colitis, asthenia, decreased neutrophil count, hypertension, increased lipase, pneumonia)	Used in previous HTA submission	Section 10.2.2
Doyle S, et al. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008;62(3):374-80.[51]	Disutility of grade 3-4 AEs for hypertension	Used in previous HTA submission	Section 10.2.2; Table 50
Tolley K, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ. 2013;14(5):749-59.[52]	Disutility of grade 3-4 AEs for pneumonia	Used in previous HTA submission	Section 10.2.2; Table 50
Mai K, et al. The diagnosis and management of endocrine side effects of immune checkpoint inhibitors. Dtsch Arztebl Int. 2021 Jun 11;118(Forthcoming):389-96.[53]	Disutility of grade 3-4 AEs for hypophysitis, adrenal insufficiency, and hyperthyroidism	Used in previous HTA submission	Section 10.2.2; Table 50

6 Efficacy

6.1 Efficacy of NIVO+IPI compared with PEMBRO for the first-line treatment of patients with dMMR/MSI-H mCRC

6.1.1 Relevant studies

6.1.1.1 CheckMate 8HW

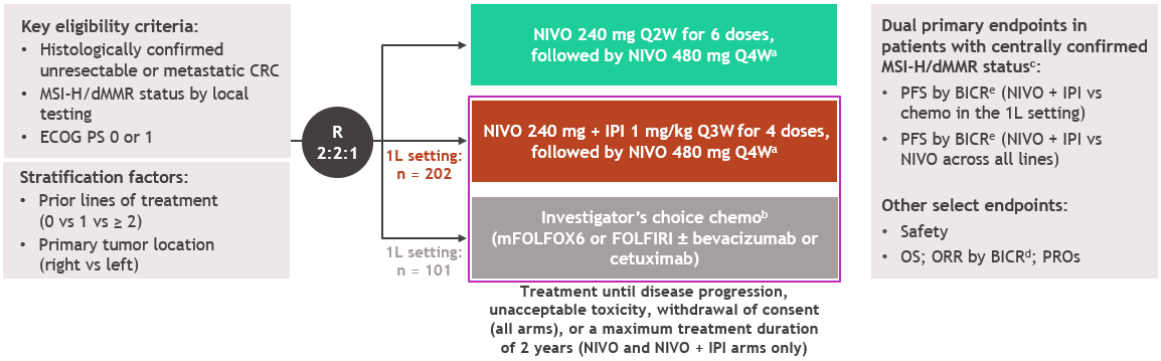
The comparison of NIVO+IPI with PEMBRO is based on the CM 8HW and KN-177 trials, which are included here and used to inform the indirect treatment comparison (ITC) described in Section 7.

CM 8HW (NCT04008030) is a phase 3 randomised controlled trial evaluating NIVO+IPI or NIVO monotherapy versus chemotherapy in patients with dMMR/MSI-H mCRC.[10,41-43] The primary objectives are (1) to compare the clinical benefit of NIVO+IPI versus chemotherapy as first-line treatment of participants with dMMR/MSI-H mCRC and (2) to compare the clinical benefit of NIVO+IPI with NIVO monotherapy in all lines of treatment in participants with dMMR/MSI-H mCRC.[10] The current indication under review is based on the first objective in only the first-line setting; therefore, the NIVO+IPI and chemotherapy arms are the focus of this dossier, and the NIVO monotherapy arm is included only as supportive evidence. For the comparison of NIVO+IPI versus chemotherapy, the results are based on the 12 October 2023 data cutoff, which only included the NIVO+IPI and chemotherapy arms.

Although NIVO monotherapy is not approved by the European Medicines Agency (EMA) for this indication, the comparison of NIVO+IPI versus NIVO monotherapy provides useful supporting information. Data for the comparison of NIVO+IPI versus NIVO monotherapy in all lines recently became available based on a data cutoff on 28 August 2024 (database lock [DBL] on 25 September 2024) and are provided in the submission for completeness but are not used in the economic model.[54]

Appendix A summarises the main characteristics of CM 8HW; Figure 4 presents the CM 8HW study design for objective 1 of relevance to this submission. As noted above, the analysis of NIVO+IPI versus NIVO monotherapy included first-, second-, and third-line participants.

Figure 4. CM 8HW: study design



[a] Participants with ≥ 2 prior lines were randomly assigned to only arm A or B during part 1; only participants with 0 prior lines were randomly assigned during part 2 enrolment. [b] Participants receiving investigator's choice of chemotherapy are eligible to receive NIVO+IPI upon progression (crossover treatment). [c] Confirmed using either immunohistochemistry and/or polymerase chain reaction–based tests. [d] Evaluated using RECIST v1.1. Adapted from BMS data on file (2024)[10]

The co-primary endpoints are PFS by blinded independent central review (BICR) (centrally confirmed) achieved by NIVO+IPI in participants with dMMR/MSI-H mCRC relative to chemotherapy (in the first-line setting) or NIVO monotherapy (in any line). For the interim analysis used in the EMA application, the primary endpoint compared PFS per BICR in first-line participants with centrally confirmed dMMR/MSI-H receiving NIVO+IPI or chemotherapy. The other primary endpoint (comparing PFS per BICR in all participants with centrally confirmed dMMR/MSI-H mCRC receiving either NIVO+IPI or NIVO monotherapy) is provided only as supporting information.

Figure 5 presents the testing strategy for the primary and secondary endpoints of CM 8HW. The planned interim analysis of the co-primary endpoint of relevance to this submission (PFS per BICR for NIVO+IPI vs. chemotherapy in first-line patients; red box in Figure 5) was conducted based on number of PFS events that triggered the DBL in November 2023 (October 2023 data cutoff).[54]

Figure 5. [redacted]

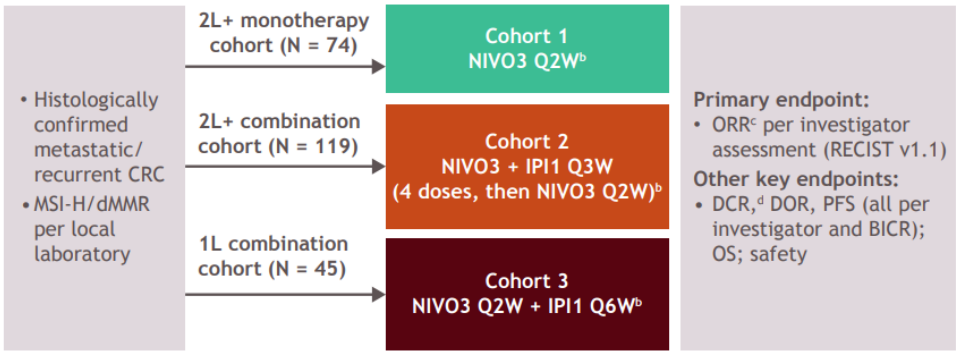
[redacted]

A second interim analysis for the second co-primary endpoint (PFS per BICR for NIVO+IPI vs. NIVO in participants receiving any line of treatment; orange box in Figure 5) was conducted based on the number of PFS events that triggered the DBL in September 2024 (August 2024 data cutoff). These data cannot directly be compared with the NIVO+IPI versus chemotherapy analysis in first-line treatment due to the inclusion of participants undergoing second- and third-line treatment; these data are included only for supporting information. A future analysis will compare NIVO+IPI with NIVO monotherapy in the first-line setting, but at the time of the September 2024 DBL, there were insufficient events (peach box in Figure 5). The statistical plan for DBLs and the very promising initial readout suggest that expediting patient access to NIVO+IPI in the first-line setting is warranted.[54]

6.1.1.2 CheckMate 142

CM 142 (NCT02060188) is a multicohort, non-randomised phase 2 study evaluating the efficacy and safety of NIVO-based therapies, NIVO+ IPI in 1L or 2L, or NIVO monotherapy, in patients with mCRC. The results are based on an analysis with a data cutoff of 15 September 2022. Appendix A summarises study characteristics; Figure 6 presents the study design.

Figure 6. CM 142[a]: study design



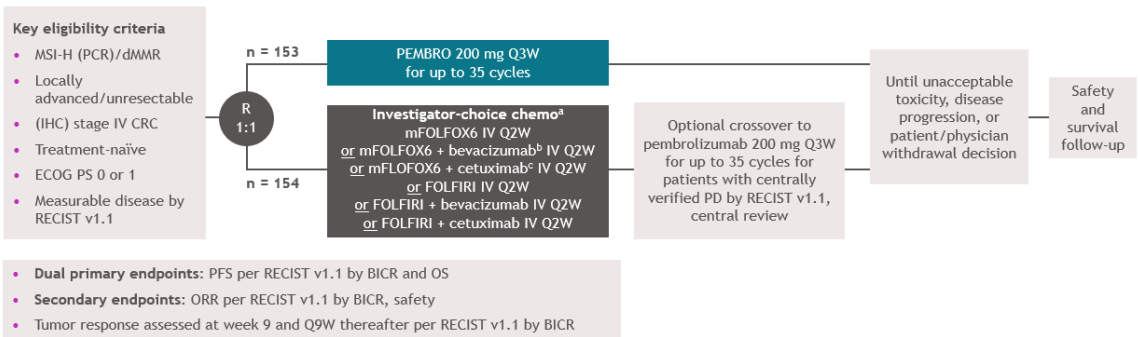
[a]ClinicalTrials.gov number, NCT02060188; [b]Until disease progression, discontinuation due to toxicity, withdrawal of consent, or maximum clinical benefit per investigator. Treatment beyond initial evidence of PD was permitted if the patient tolerated the study drug and benefited from study treatment per investigator assessment; [c]Patients with CR + PR divided by the number of treated patients; [d]Patients with CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients. Source: Overman et al. (2022)[47], Andre et al. (2022)[48].

The primary endpoint was ORR as determined by the investigator by RECIST, version 1.1. The secondary endpoints included DCR, DOR, PFS, OS, and safety, with evalutations conducted at baseline, every 6 weeks after first dose for 24 weeks, and then every 12 weeks until disease progression or treatment discontinuation.[48] CM 142 is only provided as supportive information for the CEM as it was not designed or powered to measure the comparative efficacy of NIVO+IPI in this setting.

6.1.1.3 KeyNote-177

KN-177 (NCT02563002) was the pivotal phase 3 study assessing the efficacy and safety of PEMBRO versus chemotherapy in the treatment of patients with dMMR/MSI-H mCRC. The results are based on the final analysis (data cutoff, 17 July 2023). Appendix A summarises study characteristics; Figure 7 presents the study design.

Figure 7. KN-177: study design



[a] Chosen before randomisation. [b] Bevacizumab 5 mg/kg intravenously. [c] Cetuximab 400 mg/m^2 over 2 hours, then 250 mg/m^2 intravenously over 1 hour weekly. Source: Shiu et al. (2023)[9]

Table 12 summarises the CM 8HW and KN-177 trials. In CM 8HW, at randomisation, participants were required to have confirmed MSI-H/dMMR status, determined according to local standard of practice. Tumour samples collected at screening were then sent to a central laboratory for confirmation of MSI-H/dMMR status. The prespecified primary outcome was based on this centrally confirmed subpopulation. However, the centrally

confirmed subpopulation (n = 171 [NIVO+IPI] and n = 84 [chemotherapy]) was smaller than the full population with locally confirmed dMMR/MSI-H (n = 202 [NIVO+IPI] and n = 101 [chemotherapy]), [10] which is more comparable with the population on which the KN-177 efficacy is based. Therefore, the locally confirmed (or intention-to-treat [ITT]) population in CM 8HW is the focus of the results included in this submission. Of note, four different measures of PFS were included as primary or secondary endpoints in CM 8HW; however, PFS by BICR in patients with dMMR/MSI-H status locally confirmed is the main endpoint of interest, as it is most comparable with the definition used in KN-177.

Table 12. Overview of study design for studies included in the comparison

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
CM 8HW, NCT04008030[10,42,43]	Phase 3, randomised, open-label study with 3 arms; however, only the NIVO+IPI vs. chemotherapy comparison as 1L treatment is included in the EMA label: ▪ **Arm A:** NIVO monotherapy ▪ **Arm B:** NIVO+IPI ▪ **Arm C:** investigator's choice of chemotherapy	Up to 2 years of treatment	▪ Aged ≥ 18 years with locally confirmed dMMR/MSI-H mCRC ▪ ECOG PS 0 or 1 ▪ No prior treatment for metastatic disease	▪ Arm B: NIVO 240 mg + IPI 1 mg/kg Q3W for 4 doses, followed thereafter by NIVO 480 mg Q4W	▪ Arm C: investigator's choice of FOLFOX or FOLFIRI, which could be combined with bevacizumab or cetuximab ▪ Arm A: NIVO 240 mg Q2W for 6 doses, followed by NIVO 480 mg Q4W	For the NIVO+IPI vs. chemotherapy comparison in 1L treatment, stratification factors include primary tumour location (right vs. left): ▪ Primary outcome: PFS by BICR in patients with dMMR/MSI-H status centrally confirmed. ▪ Secondary outcomes: — PFS by BICR in patients with dMMR/MSI-H status locally confirmed — PFS by investigator in patients with dMMR/MSI-H status centrally confirmed — PFS by BICR in patients with dMMR/MSI-H status centrally confirmed by each central test ▪ Median follow-up: [redacted] months with a minimum follow-up of 6.1 months (interim analysis based on a clinical data cutoff on 12 October 2023)[55] For the NIVO+IPI vs. NIVO monotherapy comparison, stratification factors include prior lines of treatment (0 vs. 1 vs. ≥ 2) and primary tumour location (right vs. left). Endpoints align with those for the primary objective. Supporting interim analysis comparing NIVO+IPI with NIVO monotherapy based on a clinical data cutoff on 28 August 2024; minimum follow-up, [redacted] months; median follow-up, [redacted] months.

Trial name, NCT number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
KN-177, NCT02563002[9,39,45]	Phase 3, open-label study of PEMBRO vs. investigator's choice of chemotherapy	Maximum of 35 cycles treatment (approximately 2 years)	▪ Aged ≥ 18 years with locally confirmed dMMR/MSI-H stage IV mCRC ▪ Treatment naive ▪ ECOG PS 0 or 1 ▪ Measurable disease by RECIST v1.1	▪ PEMBRO 200 mg Q3W for up to 2 years	▪ Investigator's choice of chemotherapy	▪ Dual primary outcomes: – PFS per RECIST v1.1 by BICR in the ITT population – OS ▪ Secondary outcomes: – ORR per RECIST v1.1 by central review – Safety and tolerability in all treated participants ▪ Median (range) study follow-up: 44.5 months (36.0-60.3) with PEMBRO vs. 44.4 months (36.2-58.6) with chemotherapy (final analysis based on interim data cutoff on 19 February 2021)[45] ▪ Median follow-up duration: 73.3 months (6.1 years; range, 64.9-89.2 months) at data cutoff on 17 July 2023[9]

6.1.2 Comparability of studies

No head-to-head data are available to compare NIVO+IPI investigated in CM 8HW versus its key comparator, PEMBRO, which was studied in KN-177. Therefore, an ITC was conducted to estimate the relative efficacy of treatments. The two trials have similar designs and are comparable in terms of inclusion and exclusion criteria, common comparator (chemotherapy) treatments, and outcome definitions. In both trials, the control arm received investigator's choice of standard chemotherapy defined as FOLFOX (5-fluorouracil + leucovorin + oxaliplatin) or FOLFIRI (5-fluorouracil + leucovorin + irinotecan) with or without bevacizumab or cetuximab, and PFS by BICR was the primary outcome. It is important to note that, in KN-177, the primary outcome was based on a population with locally confirmed dMMR/MSI-H status, whereas the primary outcome in CM 8HW, dMMR/MSI-H status, was centrally confirmed, as described in Section 6.1.1. To ensure comparability, data for the locally confirmed (ITT) population in CM 8HW are the focus of this submission.

6.1.2.1 Comparability of patients across studies

Figure 17 presents key demographic and baseline characteristics for the ITT populations of CM 8HW, CM 142 and KN-177. Key demographic and baseline characteristics were generally well balanced between the studies. Eastern Cooperative Oncology Group performance status (ECOG PS) also was balanced across the studies, with 56% to 43% patients in the intervention arms having a PS of 0.[45,47,56]

Table 13. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	CM 8HW		CM 142			KN-177	
	NIVO+IPI (n = 202)	Chemo (n = 101)	2L+ NIVO (n = 74)	2L+ NIVO+IPI (n = 119)	1L+ NIVO+IPI (n = 45)	PEMBRO (n = 153)	Chemo (n = 154)
Age, median (range), years	62 (21-86)	65 (26-87)	53 (26-79)	58 (21-88)	66 (21-85)	63 (52-73)	63 (48-72)
Gender							
Female	107 (53)	56 (55.4)	30 (41)	49 (41)	22 (49)	82 (54)	72 (47)
Male	95 (47)	45 (44.6)	44 (59)	70 (59)	23 (51)	71 (46)	82 (53)
Region							
Asia	19 (9.4)	11 (10.9)	NR	NR	NR	22 (14)	26 (17)
US/Canada/Europe	133 (65.8)	71 (70.3)	NR	NR	NR	109 (71)[a]	113 (73)[a]
Rest of world	50 (24.8)	19 (18.8)	NR	NR	NR	22 (14)	15 (10)
ECOG PS 0	111 (55)	52 (51.5)	32 (43)	54 (45)	25 (56)	75 (49)	84 (54)
Disease stage IV at initial diagnosis	85 (42.1)	49 (48.5)	33 (45)	53 (45)	17 (38)	73 (48)	80 (52)

	CM 8HW		CM 142			KN-177	
	NIVO+IPI (n = 202)	Chemo (n = 101)	2L+ NIVO (n = 74)	2L+ NIVO+IPI (n = 119)	1L+ NIVO+IPI (n = 45)	PEMBRO (n = 153)	Chemo (n = 154)
Tumour right sidedness	138 (68.3)	68 (67.3)	56 (76)	81 (68)	37 (82)	102 (67)	107 (69)
Sites of metastases[b]							
Liver	76 (37.6)	42 (41.6)	NR	NR	NR	71 (46)	54 (35)
Lung	44 (21.8)	25 (24.8)	NR	NR	NR	36 (23.5)	34 (22.1)
Peritoneum	84 (41.6)	43 (42.6)	NR	NR	NR	NR	NR
BRAF, *KRAS*, *NRAS* variant status							
BRAF/*KRAS*/*NRAS* all wild-type	47 (23.3)	23 (22.8)	29 (39)	31 (26)	13 (29)	43 (28)	38 (25)
BRAF variant	52 (25.7)	24 (23.8)	12 (16)	30 (25)	17 (38)	NR	NR
KRAS or *NRAS* variant	43 (21.3)	21 (20.8)	27 (36)	44 (37)	10 (22)	33 (22)	39 (25)
Unknown	55 (27.2)	31 (30.7)	6 (8)	14 (12)	5 (11)	42 (27)	31 (20)
Clinical history of Lynch syndrome							

	CM 8HW		CM 142			KN-177	
	NIVO+IPI (n = 202)	Chemo (n = 101)	2L+ NIVO (n = 74)	2L+ NIVO+IPI (n = 119)	1L+ NIVO+IPI (n = 45)	PEMBRO (n = 153)	Chemo (n = 154)
Yes	22 (10.9)	17 (16.8)	NR	NR	NR	NR	NR
No	135 (66.8)	49 (48.5)	NR	NR	NR	NR	NR
Reported as unknown	44 (21.8)	30 (29.7)	NR	NR	NR		

Note: Data shown are number of participants (%) unless otherwise noted. [a] Western Europe or North America. [b] Per BICR in CM 8HW. Sources: Diaz et al. (2022)[45]; Overman et al. (2022)[47], BMS data on file (2024)[56]; DMC (2021)[37]

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 14 summarises key patient characteristics in CM 8HW. These values are used in the health economic model. No Danish real-world evidence data specific to people with dMMR/MSI-H mCRC are available; therefore, the characteristics from CM 8HW are assumed to be representative of the population in Denmark.

Table 14. CM 8HW: characteristics in the relevant Danish population and the health economic model

	Value in Danish population	Value used in health economic model (CM 8HW)
Age (years)	NA	60.9
Gender (female, %)	NA	53.8
Patient weight (average, kg)	NA	70.5
Mean body surface area (m^2)	NA	1.8

Sources: BMS data on file (2024)[56]; BMS data on file (2024)[56]

6.1.4 Efficacy: results per CM 8HW comparison of NIVO+IPI with chemotherapy as first-line therapy

The results summarised in this submission are from interim analysis 1 of CM 8HW based on a clinical data cutoff on 12 October 2023. At the time of the data cutoff, the minimum follow-up was [redacted] months, and the median follow-up was [redacted] months.

The PFS per BICR results for all first-line randomly assigned participants (locally confirmed; ITT population; secondary endpoint) favoured NIVO+IPI over chemotherapy (hazard ratio [HR], [redacted]; 95% confidence interval [CI], [redacted]). The median PFS was [redacted] (95% CI, [redacted] to [redacted] for participants treated with NIVO+IPI versus those treated with chemotherapy ([redacted] months; 95% CI, [redacted]) (Table 15 and Figure 8).[56]

Table 15. CM 8HW: PFS per primary definition per BICR (all first-line randomly assigned participants in arm B vs. arm C)

	Arm B: NIVO+IPI (n = 202)	Arm C: Chemo (n = 101)
Events/participants (%)	[redacted]	[redacted]
Median PFS (months) (95% CI)[a]	[redacted]	[redacted]
HR (95% CI)[b]	[redacted]	

Note: Excludes data collected on or after first crossover dose date. [a] Based on Kaplan-Meier estimates. [b] HR is arm B over arm C from a Cox model stratified by tumour sidedness (left vs. right) as entered in the interactive response system. Source: BMS data on file (2024)[56]

Figure 8. CM 8HW: KM plot of PFS per primary definition per BICR (all first-line randomly assigned participants in arms B and C)

Notes: Statistical model for hazard ratio and *P* value: stratified Cox proportional hazard model and stratified log-rank test by tumour sidedness (left vs. right) as entered in the interactive response system. Excludes data collected on or after first crossover dose date. KM plot will be generated only if there are ≥ 10 participants in each treatment arm in the population or subgroup. Source: BMS data on file (2024)[57]

The PFS rates were [redacted] at 12 and 24 months in the NIVO+IPI arm compared with [redacted] PFS in the chemotherapy arm, respectively (Table 16).[56]

Table 16. CM 8HW: PFS per primary definition rates per BICR (all first-line randomly assigned participants in arm B and C)

PFS rate (95% CI)	NIVO+IPI (n = 202)	Chemo (n = 101)
At 6 months	[redacted]	[redacted]
At 12 months	[redacted]	[redacted]
At 24 months	[redacted]	[redacted]

Notes: Based on Kaplan-Meier estimates. Minimum follow-up is defined as time from clinical cutoff date to last participant's randomisation date. Excludes data collected on or after first crossover dose date. Source: BMS data on file (2024)[56]

Overall survival data are not yet available for CM 8HW.

Figure 9 presents subgroup analyses for PFS in the population of patients with locally confirmed dMMR/MSI-H. The efficacy benefit observed in the overall population also is seen in all prespecified subgroups, including patients with and without metastases, and regardless of PD-L1 expression levels and the status of other genetic variants. However, these data should be interpreted with caution, as patient numbers in some of these subgroups were low.

Figure 9. CM 8HW: forest plot for PFS per primary definition per BICR (all participants with locally confirmed dMMR/MSI-H status in arm B vs. arm C) by key subgroups

Source: BMS data on file (2024)[58]

6.1.5 Efficacy: results in KN-177

The results summarised here are from the final analysis of KN-177. At the time of data cutoff for final analysis on 17 July 2023, the median study follow-up was 73.3 months (range 64.9-89.2 months).[44]

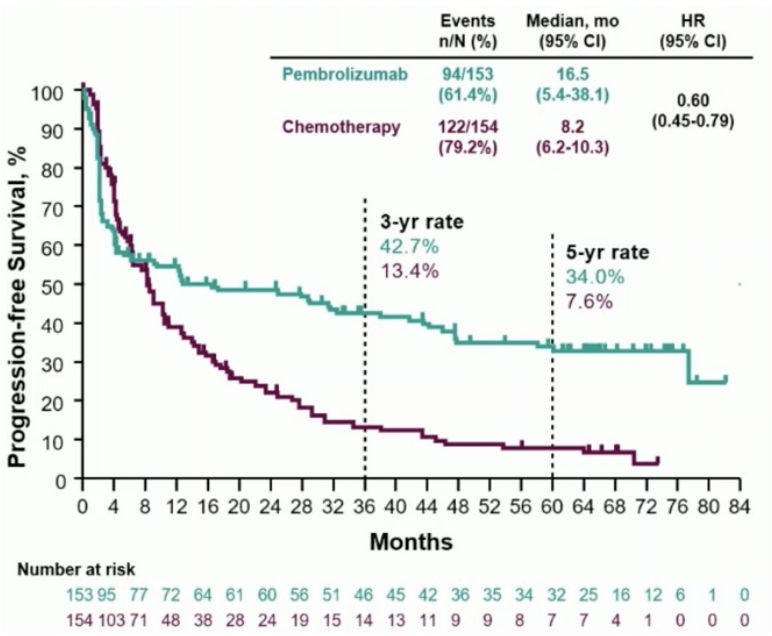
PEMBRO resulted in longer PFS versus chemotherapy in participants with dMMR/MSI-H mCRC. The median PFS was 16.5 months (95% CI, 5.4-38.1) with PEMBRO versus 8.2 months (95% CI, 6.2-10.3) with chemotherapy (HR, 0.60; 95% CI, 0.45-0.79) (Table 17 and Figure 10).[9,44]

Table 17. KN-177: PFS per primary definition per BICR at the final analysis (17 July 2023 data cutoff)

	PEMBRO (n = 153)	Chemo (n = 154)
Events/participants (%)	94/153 (61.4)	122/154 (79.2)
Median PFS (months) (95% CI)	16.5 (5.4-38.1)	8.2 (6.2-10.3)
HR (95% CI)	0.60 (0.45-0.79)	

Sources: Shiu et al. (2023)[9]; Shiu et al. (2023)[44]

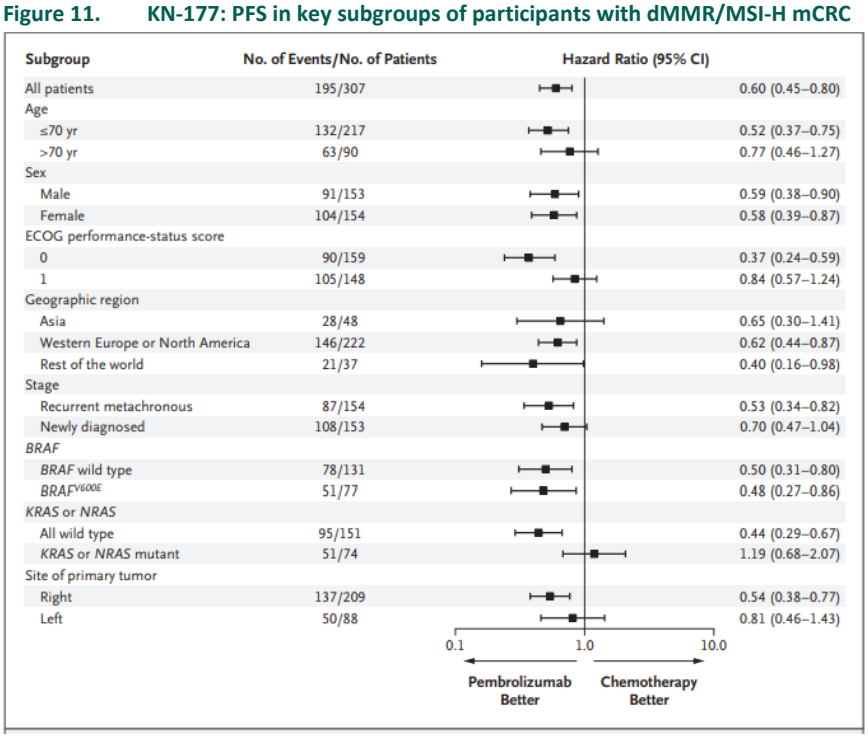
Figure 10. KN-177: KM estimates of PFS at July 2023 data cutoff



Note: Time from randomisation to first disease progression, as assessed by central review according to RECIST, v1.1, or death from any cause. Source: Shiu et al. (2023)[44]

Progression-free survival was consistently longer with PEMBRO than with chemotherapy across key prespecified subgroups in the ITT population (Figure 11).[39] Data from the final data cutoff were not identified; therefore, subgroup data from the 19 February 2021 analysis are presented. Of note, the HR for all patients remained consistent between the two analyses.

Figure 11. KN-177: PFS in key subgroups of participants with dMMR/MSI-H mCRC



Source: Andre et al. (2020)[39]

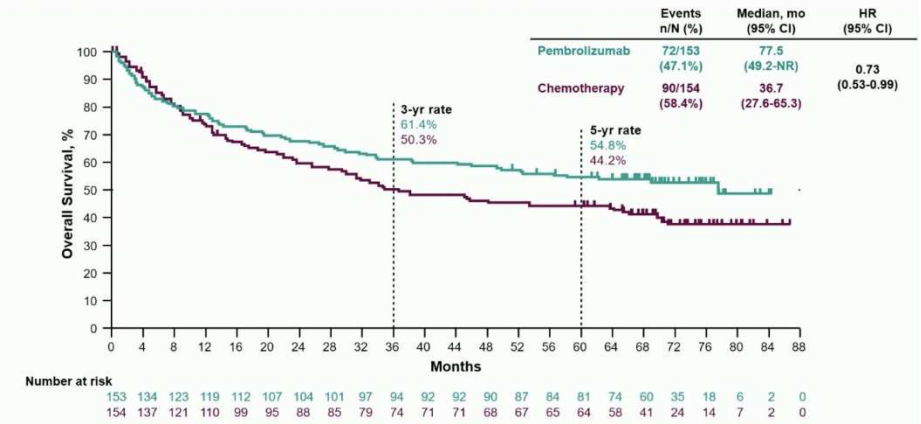
PEMBRO resulted in longer OS versus chemotherapy in participants with dMMR/MSI-H mCRC (Table 18 and Figure 12). The 5 year OS rate was 54.8% in the pembro arm and 44.2% in the chemo arm (Figure 12).

Table 18. KN-177: OS at the final analysis (17 July 2023 data cutoff)

	PEMBRO (n = 153)	Chemo (n = 154)
Events/participants (%)	72/153 (47.1)	90/154 (58.4)
Median OS (months) (95% CI)	77.5 (49.2-NR)	36.7 (27.6-65.3)
HR (95% CI)	0.73 (0.53-0.99)	

Sources: Shiu et al. (2023)[9]; Shiu et al. (2023)[44]

Figure 12. KN-177: KM estimates of OS at July 2023 data cutoff



Source: Shiu et al. (2023)[44]

6.1.6 Efficacy: results in CM 142

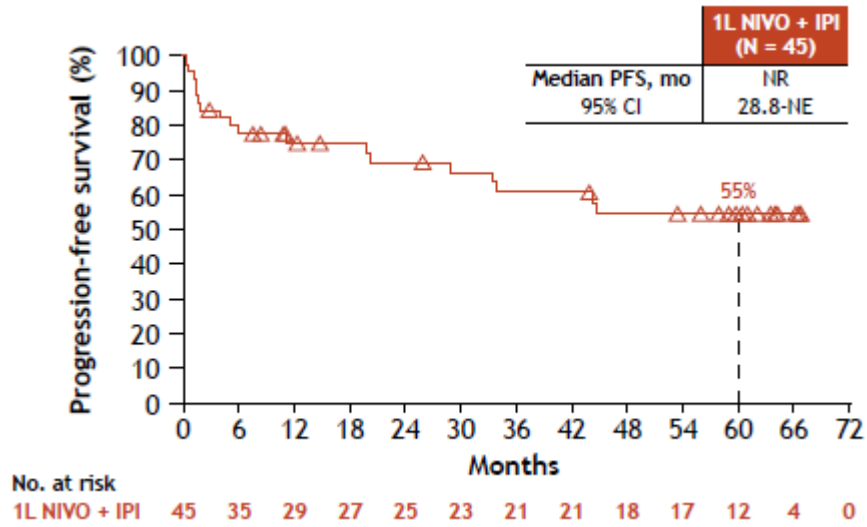
For CM 142, for PFS, at data cutoff on August 2020, median duration of follow-up was 50.9 months (range 46.9-62.7 months). The median PFS for the NIVO+IPI cohort was not reached.{Andre, 2022 #139} At the database lock on September 15, 2022, when median follow-up was 64.2 months (range 59.4-68.9 months), median PFS had still not been reached (NR (95% CI 28.8-NE) (Table 19 and Figure 13).[46]

Table 19. 1st line CM 142 NIVO+IPI cohort: PFS per Investigator assessment (15 September 2022 data cutoff)

	NIVO+IPI (n = 119)
Median PFS (months) (95% CI)	NR (22.8-NE)

Source: Lenz et al. (2024)[46]

Figure 13. **1st line CM 142 NIVO+IPI cohort: KM estimates of PFS at 15 September 2022 data cutoff**



Note: Time from randomisation to first disease progression, as assessed by central review according to RECIST, v1.1, or death from any cause. Source: Lenz et al. (2024)[46]

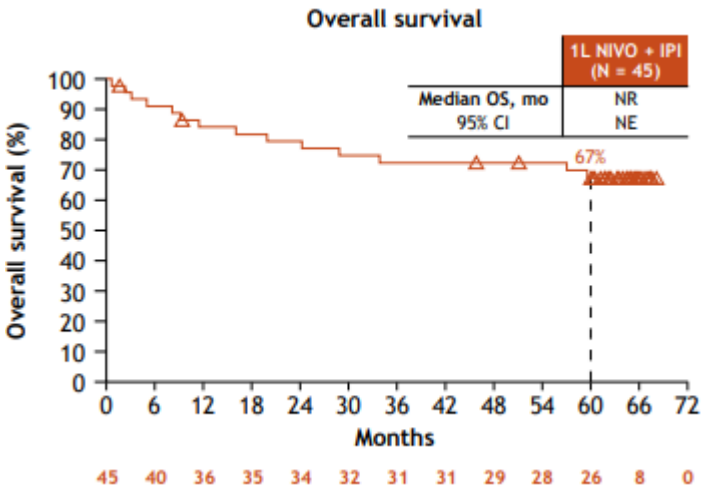
At the data cutoff on September 15, 2022, , the median OS was not reached for the NIVO+IPI cohort, at 60 months the OS rate was 67% (Table 20 and Figure 14).

Table 20. **1st line CM 142 NIVO+IPI cohort: OS at the 64 month analysis (15 September 2022 data cutoff)**

	NIVO+IPI (n = 45)
Median OS (months) (95% CI)	NR (NE)

Source: Lenz et al. (2024)[46]

Figure 14. **1st line CM 142 NIVO+IPI cohort: KM estimates of OS at September 2022 data cut-off**



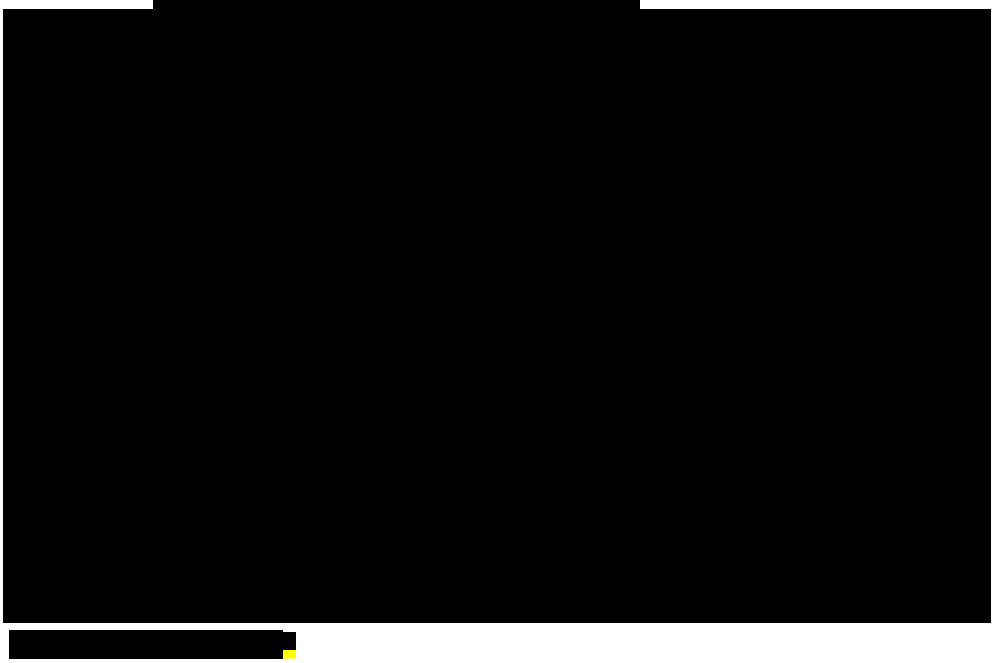
Source: Lenz et al. (2024)[46]

6.1.7 CM 8HW comparison of NIVO+IPI with NIVO monotherapy in any line of therapy

The efficacy results for the supporting analysis of NIVO+IPI versus NIVO monotherapy in any line of therapy are from interim analysis 2 of CM 8HW based on a clinical data cutoff on 28 August 2024. At the time of the data cutoff, the minimum follow-up was [redacted] months and the median follow-up was [redacted] months.[54]

The PFS per BICR results for all randomly assigned participants (locally confirmed, ITT population, any line of therapy) favoured NIVO+IPI over NIVO monotherapy (HR, [redacted]; 95% CI, [redacted]). The median PFS was [redacted] months (95% CI, [redacted] months-[redacted]) for participants treated with NIVO+IPI versus [redacted] months (95% CI, [redacted] months) for those treated with NIVO monotherapy (Figure 15).[56]

Figure 15. [redacted]



As detailed above, this interim analysis is provided only for information. NIVO monotherapy is not licensed in this indication, and the available results are for all lines of therapy, whereas NIVO+IPI is licensed only as a first-line treatment in this indication. Nonetheless:

- NIVO+IPI demonstrates a consistent efficacy benefit over NIVO monotherapy in this multiple-line therapy setting.
- The HR for this comparison ([redacted]) is similar to the HR reported in the unanchored analysis comparing NIVO+IPI in CM 8HW with PEMBRO in KN-177, both before and after weighting (Section 7.1.3.1, Table 22). This validates the ITC results of dual IO therapy versus IO therapy in mCRC (but in the broader setting of multiple lines of therapy).

Insufficient events have occurred to allow a comparison of NIVO+IPI with NIVO monotherapy in the first-line setting. However, additional analyses are planned. In the

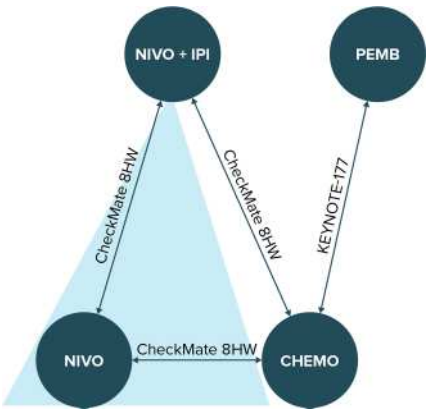
meantime, the data available for a comparison of NIVO+IPI with NIVO monotherapy support the additional benefit of the IO-IO combination and the comparisons of NIVO+IPI versus chemotherapy and the indirect comparison with PEMBRO that support the economic model.

7 Comparative analyses of efficacy

No head-to-head data are available to compare NIVO+IPI, investigated in CM 8HW, with PEMBRO, which was studied in KN-177. Therefore, an ITC was conducted to estimate the relative efficacy of treatments. The key methods, analyses, and outcomes used for the base-case health economic model are presented in this section; Appendices C and D present a comprehensive description of the ITC analysis performed.

Based on the comparators of interest and study populations, KN-177, a phase 3 randomised controlled trial, has been identified as the only 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 CM 8HW with KN-177 via the common comparator chemotherapy (Figure 16).

Figure 16. Network of evidence



Note: Data for NIVO monotherapy are not available in the October 2023 data cutoff of CM 8HW. Hence, the feasibility assessment includes only NIVO+IPI and chemotherapy arms from the trial.

For a description of assessment of proportional treatment effect with time see Appendix C8.1.1.

7.1.1 Differences in definitions of outcomes between studies

The similarity assessment revealed that CM 8HW 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 with only minor differences noticed in the distribution of the race of patients, with CM 8HW having a greater proportion of White and fewer Asian patients compared with KN-177.

However, a difference in the primary outcome definition was observed because the study population in KN-177 was based on locally confirmed dMMR/MSI-H status,

whereas, in CM 8HW, dMMR/MSI-H status was centrally confirmed. This difference may affect the results, as it has been shown in CM 8HW that the efficacy differs for locally misdiagnosed dMMR/MSI-H.[59]

Thus, to ensure comparability, data for the locally confirmed (ITT) population in CM 8HW were used for the analysis. Furthermore, as imbalances in treatment effect modifiers (TEMs) between trials were identified, such as differences between the regional distributions, the CM 8HW data were reweighted via MAIC methodology such that the distribution in TEMs in CM 8HW matches that in KN-177.

7.1.2 Method of synthesis

To avoid introducing potential bias into the ITC, the distribution of TEMs (baseline characteristics that modify the effect of treatment) across trials was carefully assessed. Any imbalance in this distribution could breach the transitivity assumption of the ITC. Potential TEMs were identified based on subgroup analyses of forest plots for CM 8HW and KN-177 for the outcome of interest (PFS) (see Section 6.1.4).

However, not all information was available for KN-177 (e.g., the share of centrally confirmed patients, the percentage of patients with a < 1% tumour cell PD-L1 expression, the number of patients with Lynch syndrome, or the percentage of patients with peritoneal metastases), which limited the comparison and potential adjustment of the TEMs. The following seven TEMs were finally identified for matching based on the forest plots and availability of published data from KN-177: age, ECOG performance score, BRAF/KRAS/NRAS variant status, side of primary tumour (left or right), liver metastasis, liver or lung metastasis, and region. The distribution of the identified potential TEM variables across trials appears to be relatively comparable for most of the TEMs, with differences between trials ≤ 3%. For the variable of region, differences are visible, with CM 8HW having fewer patients from Asia and Western Europe/North America but more from the rest of the world. Therefore, based on the identified heterogeneity, a method adjusting for differences between populations was seen as the most appropriate method for the analysis.

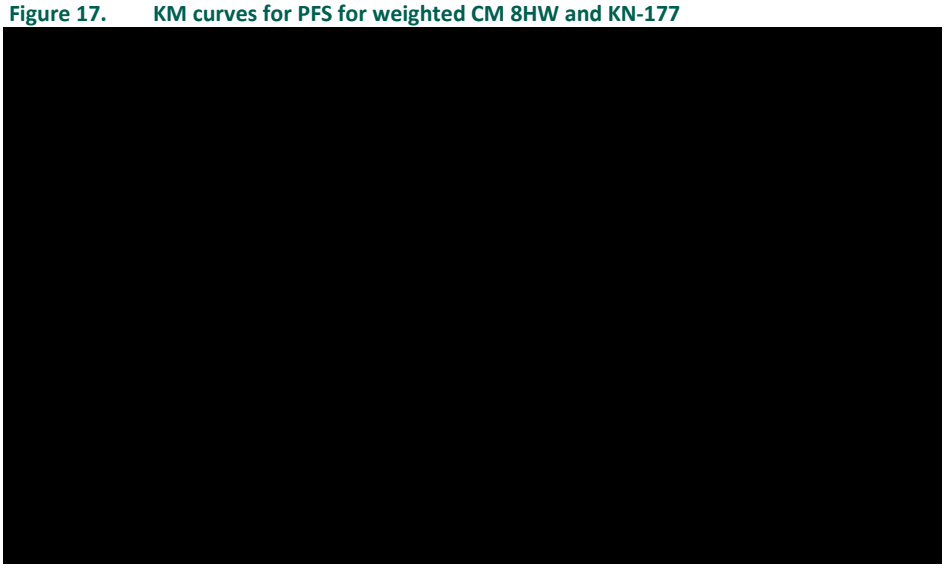
In general, anchored MAIC is the preferred method in these cases, relying on fewer assumptions compared with the unanchored MAIC, as randomisation is preserved. MAIC is a population-adjusted treatment comparison method to adjust for cross-study differences in clinically relevant TEMs. MAIC recalculates the efficacy of the treatment (i.e., NIVO+IPI), assuming the treatment is used in patient populations similar to those of the respective comparator trial (i.e., population of KN-177). The MAIC methodology is described in detail in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document 18.[60] The matching methodology is designed to statistically construct trial patient populations that are like one another so that the outcomes from the trials can be meaningfully compared.

Population adjustment is done using the IPD from one study to match the population of the other study. CM 8HW was matched to the pseudo-IPD from KN-177 by means of anchored MAIC. Anchored indirect comparisons between two treatments rely on the presence of a common comparator; in this case, the chemotherapy arms of both trials were

used as a common comparator. Randomisation within each trial ensures bias is omitted due to imbalanced prognostic variables across the trials. TEMs are not controlled for through randomisation and will introduce bias in the estimated relative treatment effect should they not be corrected for. Therefore, these TEMs are matched in the MAIC methodology. By matching on TEMs, the CM 8HW patient population is reweighted such that the resulting population aligns with the KN-177 population regarding the TEM distribution, and their outcomes can be compared.

Given the methodological preference for an anchored MAIC, such analyses were performed (see Appendix C). However, the anchored analysis conducted appeared to be unable to fully match the chemotherapy comparator arms across studies (Figure 17), with the chemotherapy arm of CM 8HW displaying a poorer PFS than the KN-177 chemotherapy arm, even after matching. Potential causes could include an imbalance of TEM that could not be matched. For example, the share of peritoneal metastases was not reported for KN-177; however, it was high in CM 8HW (42%), and this factor is associated with a poorer prognosis and less response to systemic chemotherapy.[61] Yet, if the matching does not lead to a "common comparator," the anchored analysis results may be biased. Therefore, an unanchored MAIC matching the NIVO+IPI trial arm in CM 8HW to the PEMBRO trial arm in KN-177 in terms of TEMs and prognostic variables was chosen as the preferred analysis.

Figure 17. KM curves for PFS for weighted CM 8HW and KN-177



The unanchored MAIC methodology is similar to the methodology described above for the anchored analyses. However, there are two key distinctions. First, while the anchored analyses match the full trial population of interest (e.g., CM 8HW), the unanchored analyses match only the intervention arm populations of interest (e.g., NIVO+IPI). Second, as randomisation is preserved in the anchored analyses via the common comparator, only TEMs need to be accounted for in the matching. However, as randomisation is not persevered in the unanchored analyses, the unanchored analyses require an adjustment for TEMs and prognostic variables. To identify relevant prognostic variables, the recommended set of variables (N = 14) from the "Consensus statement on essential patient characteristics in systemic treatment trials for metastatic colorectal cancer: Supported by the ARCAD Group"[62] has been considered. Although the publication identifies

further sets of variables (with lower importance), only the recommended set of variables was analysed due to the limited sample size available in the NIVO+IPI CM 8HW arm and potential overfitting issues. Of these 14 recommended variables, 12 were already incorporated/accounted for as TEM/unavailable for KN-177 or not relevant for the population. However, two prognostic variables were added to the matching variables: (1) prior chemotherapy (yes vs. no), and (2) synchronous versus metachronous metastasis. For CM 8HW, patients were defined as having synchronous metastasis if they had disease stage at initial diagnosis (stage IV). Although both the anchored and unanchored analyses use a similar methodology, it is important to note that, in unanchored analyses, the matching was conducted specifically for the NIVO+IPI arm.

Table 21 presents the selection of additional prognostic variables for the unanchored analysis.

Table 21. Recommended variables set (N = 14)

#	Variable in the recommended set of Goey et al. (2018)[62]	Addition/reason against addition
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]

7.1.3 Results from the comparative analysis

The following sections present the results of the population-adjusted unanchored MAIC. Section 7.1.3.1 provides an overview of the population matching, and Section 7.1.4 presents the results of the time-varying HR analyses.

7.1.3.1 Unanchored analysis: matching NIVO+IPI in CM 8HW to PEMBRO in KN-177

[redacted] TEMs [redacted] and [redacted] prognostic variables [redacted] were included in the MAIC, matching the NIVO+IPI arm of CM 8HW to the KN-177 PEMBRO population. The effective sample size (ESS) was [redacted] ([redacted]% of the actual unweighted NIVO+IPI sample size). The propensity score weights ranged from [redacted] to [redacted], indicating no extreme weights being generated (see Appendix C for details). When comparing the weighted and unweighted KM curves, weighting did not change the survival estimates significantly (Figure 18). The weighted and unweighted NIVO+IPI curves follow each other closely throughout the duration of follow-up. Both the weighted and unweighted NIVO+IPI curves show higher PFS than PEMBRO from 3 months onwards. Furthermore, when comparing NIVO+IPI with PEMBRO via Cox HR (Table 22), both the weighted and unweighted analyses find similar and more favourable outcomes for NIVO+IPI.

Figure 18. KM plots of NIVO+IPI from CM 8HW (before and after matching) and PEMBRO from KN-177

Table 22. HRs and 95% CI for NIVO+IPI versus PEMBRO before and after matching

NIVO+IPI vs. PEMBRO (Cox proportional hazards–based)	HR (95% CI)
Unweighted	[redacted]
Weighted to PEMBRO	[redacted]

7.1.4 Efficacy: results per PFS of NIVO+IPI versus PEMBRO based on time-varying HRs

As the PHA is likely violated for the NIVO+IPI and PEMBRO PFS comparison, seven independent parametric survival distributions were fit to the weighted NIVO+IPI and PEMBRO data. Appendix C provides a full description of the methods and results of the survival analysis. The results from the survival curve fitting and selection of best-fitting distribution for each trial are detailed below. Of note, to avoid relative efficacy being influenced by the choice/attributes of different distributions, a common distribution for both arms was selected.

From the seven parametric survival distributions fitted to both arms, the generalised gamma had the lowest Akaike information criteria (AIC) and Bayesian information criteria (BIC) in the NIVO+IPI arm and the PEMBRO arm, respectively (see Appendix C). None of the other distributions were statistically comparable. In the combined AIC and BIC scores (summed scores across arms), generalised gamma had the least AIC and BIC with no comparable distributions based on statistical fit.

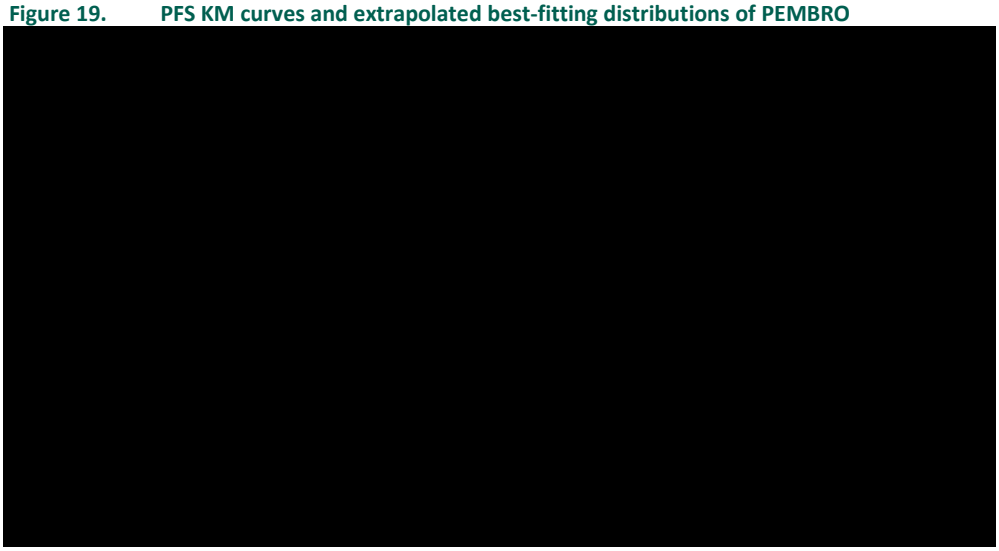
Based on the visual assessment of fit (see Appendix C), all except exponential distribution showed acceptable fit to the observed data in the NIVO+IPI arm with generalised gamma appearing to follow the observed data the best. The PEMBRO arm was similar: all the distributions tracked the observed data well except the exponential distribution, with generalised gamma appearing to represent the observed data best. Generalised gamma also provided good fit with regards to the smooth hazards for both trials (see Appendix C).

On long-term extrapolations, exponential distribution showed the worst fit while Gompertz showed the most optimistic long-term survival in the NIVO+IPI and PEMBRO arms.

Based on the visual assessment of fit, smooth hazards, and statistical fits of the parametric survival models (see Appendix D), generalised gamma is the best-fitting distribution to model PFS for NIVO+IPI and PEMBRO. The 5- and 10-year landmark survivals predicted by the distributions are [redacted] and [redacted] respectively, for the NIVO+IPI arm and [redacted] and [redacted] for the PEMBRO arm. The predicted PFS for the NIVO+IPI arm is comparable to the estimated PFS of [redacted]% ([redacted] for NIVO+IPI in first-line treatment of patients with mCRC in the CM 142 trial. The predicted 5-year estimates for KN-177 fit the published 5-year survival data (34.0% for PEMBRO).[9]

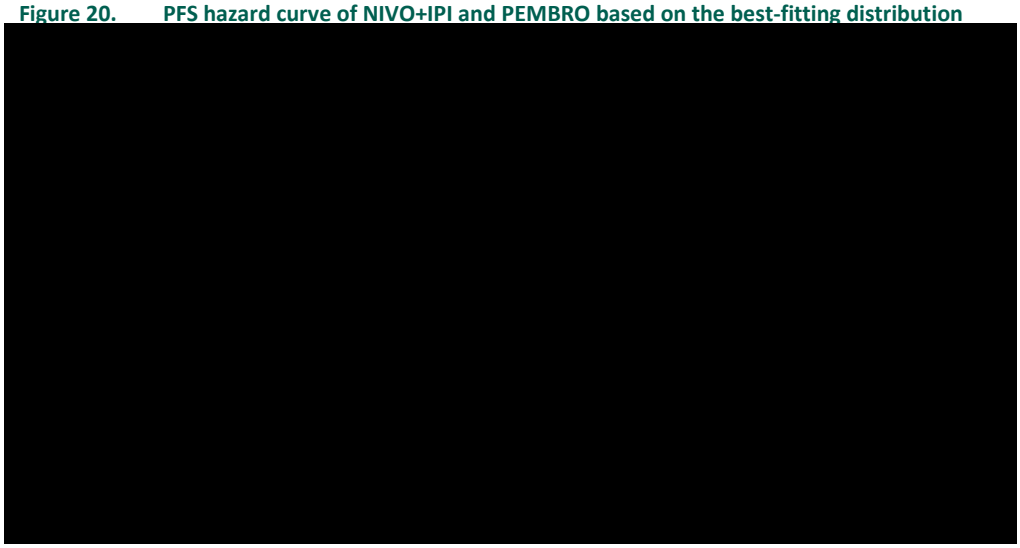
Figure 19 presents the PFS KM curves for weighted NIVO+IPI and PEMBRO, as well as the long-term extrapolation based on the best-fitting generalised gamma distribution. For comparison, the figure also presents the extrapolated survival of NIVO+IPI of the anchored ITC analysis, which predicted a comparable, however slightly higher, PFS over time.

Figure 19. PFS KM curves and extrapolated best-fitting distributions of PEMBRO



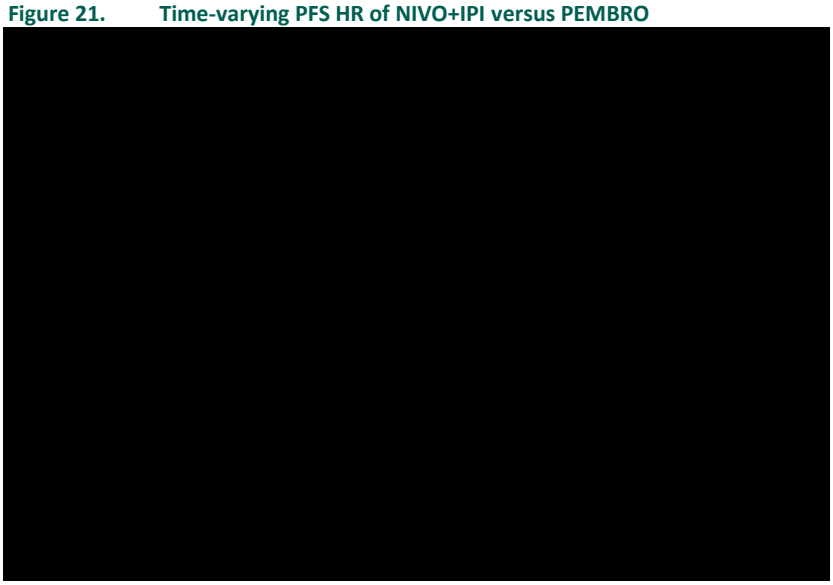
The fitted parametric distributions were used to estimate hazards and their standard errors over time. Both hazards display an initial peak and then continuously decrease after 3 months (Figure 20).

Figure 20. PFS hazard curve of NIVO+IPI and PEMBRO based on the best-fitting distribution



Based on the hazards, time-varying HRs for each timepoint of the extrapolation were estimated along with their 95% CIs (Figure 21 and Table 23). The point estimate of the time-varying HR is lower than 1 over the estimated 10-year period, meaning there were favourable results for NIVO+IPI compared with PEMBRO.

Figure 21. Time-varying PFS HR of NIVO+IPI versus PEMBRO



Note: The green dotted line represents the estimated HR for NIVO + IPI vs. PEMBRO based on the Cox HR.

Table 23. Results from the comparative analysis of NIVO+IPI versus PEMBRO for patients with mCRC

			Results using time-varying HR (95% CI)	
Outcome measure	**NIVO+IPI (n = 136.47)**	**PEMBRO (n = 153)**	**Time (in months)**	**HR (95% CI)**
Median PFS (95% CI)			0	
			12	
			24	
			36	
			48	
			60	
			72	
			84	
			96	
			108	
			120	

8 Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

To enable modelling of a lifetime perspective in the cost-effectiveness model, IPD from the CM 8HW and CM 142 trials were analysed to project survival beyond the trial period, using predicted survival to estimate transition probabilities for each health state. This section provides an overview of the data and assumptions used for the modelling of efficacy. More details can be found in Appendices C and D.

To estimate time to progression (TTP) from Progression Free (PF) to Progressed Disease (PD) ($p_{1,2}$), data from CM 8HW were used. As detailed in Section 6, this trial compared the efficacy of NIVO+IPI against chemotherapy. However, because chemotherapy is not a comparator in the current analysis, extrapolations were only conducted for the NIVO+IPI arm for the base-case analysis. The relative survival for the comparator of interest, PEMBRO, was informed based on the MAIC comparing PEMBRO with NIVO+IPI presented in Section 7.

Estimation of TTP of transitions from PF to Death ($p_{1,3}$) used background mortality data in the base-case scenario, as PF-to-Death ($p_{1,3}$) data from CM 142 were immature and thus led to unreliable extrapolations. Specifically, only 16 events occurred over the duration of CM 142 (Figure 22) for 164 participants originally at risk; thus, PF-to-Death ($p_{1,3}$]),) data from CM 142 were considered to be immature. Additionally, it was assumed that PF to Death ($p_{1,3}$) would not vary widely between treatment arms, which was also observed in CM 142 (Figure 23).

Figure 22. KM curves of PF-to-Death ($p_{1,3}$) transition for NIVO+IPI in CM 142

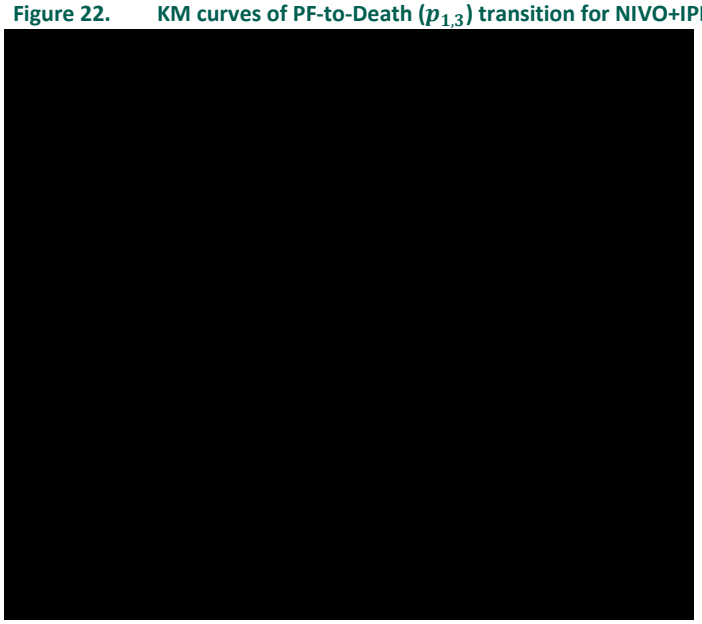
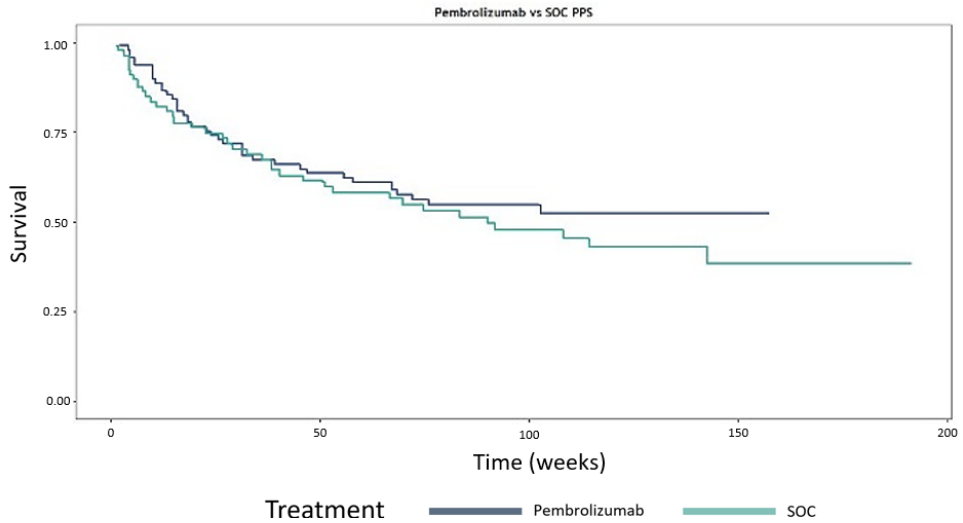


Figure 23. KM curves of PF-to-Death ($p_{1,3}$) transition for all cohorts in CM 142

For estimation of postprogression survival (i.e., from PD to Death [$p_{2,3}$]), CM 142 data were used in lieu of CM 8HW data. CM 8HW OS data were unavailable at the time of analysis, as CM 8HW had not met its primary endpoint (i.e., immature data) and was still blinded. This assumption aligns with that made in TA709,[63] which compared the efficacy of PEMBRO against chemotherapy for first-line patients with MSI-H/dMMR mCRC. The submission assumed equal postprogression survival between PEMBRO and chemotherapy, as OS for the KN-177 trial was immature. The assumption made in TA709 was accepted by the Evidence Review Group (ERG), who found that the company's simplified assumption of equal postprogression survival for all treatment arms in the model may be acceptable compared with adjusting for OS through crossover adjustment due to the immaturity of their OS data.[63] As the target patient populations of KN-177 and CM 8HW are similar and the interventions in both trials are both IO therapies, it could be argued that the approach applied in TA709 with respect to accounting for immature OS data could also be used in this study. The same assumption of equal postprogression survival has also been used in previously approved appraisals by DMC in other cancer indications[64]. Additionally, exploratory work on the postprogression outcomes in the Canada's Drug Agency (CDA-AMC) submission for PEMBRO[65] was conducted to determine if this assumption held. In this analysis, cumulative hazard curves from the PEMBRO submission to the CDA-AMC were digitised and transformed to obtain the estimated postprogression survival of the PEMBRO and chemotherapy arms. Of note, extrapolations could not be fit for this analysis because the numbers at risk for each treatment arm could not be derived from the published CDA-AMC submission. Based on this analysis, it was found that the postprogression survival between patients receiving PEMBRO and chemotherapy was comparable (Figure 24), implying that the assumption made above would hold.

Figure 24. KM curves of exploratory postprogression analysis of KN-177 data



Please find below the landmark survival estimates for the post-progression survival (PPS) curves for Pembro and chemotherapy. We have gotten out the landmark estimates for 6, 12, 24, and 36 months.

Treatment	6 months (%)	12 months(%)	24 months (%)	36 months (%)
Pembro	74.1%	63.7%	52.5%	52.5%
Chemotherapy	74.8%	58.3%	47.8%	38.5%

For context, the curves below were derived from an exploratory analysis of PPS of patients in KEYNOTE-177 that was conducted to determine if the assumption of equal PPS held. In this analysis, cumulative hazard curves from the Pembro submission to the Canadian Agency for Drugs and Technology in Health (CADTH) were digitised and transformed to obtain the estimated PPS of the Pembro and chemotherapy arms in KEYNOTE-177. Note that extrapolations could not be fit for this analysis as the numbers at risk for each treatment arm could not be derived from the published CADTH submission. Please also note that the landmark estimates derived from this method should be treated with caution, as they were reconstructed from a cumulative hazard PPS curve.

Table 24 presents an outline of the sources for each health-state transition.

Table 24. Source for the health-state transitions per treatment

Health state (from)	Health state (to)	NIVO+IPI	PEMBRO
Progression Free	Progressed Disease	TTP CM 8HW	TTP CM 8HW and HR of PEMBRO vs. NIVO+IPI based on MAIC using PFS from KN-177 and TTP from CM 8HW[a]

Health state (from)	Health state (to)	NIVO+IPI	PEMBRO
	Death	Background mortality	
Progressed Disease	Death	CM 142 and background mortality	

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of PF-to-PD transition

Extrapolation of PF-to-PD transition for NIVO+IPI

For NIVO+IPI, the transition from PF to PD ($p_{1,2}$) was estimated by fitting parametric models to the TTP data from CM 8HW (Figure 25).

Figure 25. CM 8HW: KM curve presenting the PF-to-PD transition ($p_{1,2}$) for the NIVO+IPI and chemotherapy arms

As previously noted, only the NIVO+IPI arm of CM 8HW is relevant to the current analysis. As such, use of survival analysis based on independent modelling of the NIVO+IPI arm was most suited. The models fit to data composed of standard parametric models as outlined in NICE DSU 14[66] and 21.[67] Exponential, generalised gamma, Gompertz, gamma, Weibull, log-logistic, and log-normal distributions were fit to the NIVO+IPI arm from CM 8HW. Figure 26 presents the resulting extrapolations. The best model fit was selected based on the model selection algorithm outlined in Palmer et al. (2023)[68] as well as via statistical tests such as AIC and BIC.

Due to a higher number of events being observed early in the trial as opposed to after longer follow-up, the “hockey stick” shape was observed for the TTP data of NIVO+IPI. This may be because participants had progressed before the treatment had a chance to be effective. Survival curves with this shape are difficult for some parametric distributions to fit, particularly those with too few parameters to adjust to the curve shape.

Based on AIC and the plausibility of extrapolation (see Appendix D for details), the generalised gamma model was chosen as the best option for NIVO+IPI.

The generalised gamma model was chosen to extrapolate TTP for NIVO+IPI for the following reasons:

- Its fit to the observed data based on AIC: The AIC value for the generalised gamma model is significantly lower (989.4 vs. 1,012.8 for log-normal and 1,019.8 for log-logistic). The smoothed hazard plots also support this, as the generalised gamma fit provides the closest fit to the hazards estimated in the NIVO+IPI arm.
- Performance relative to other parametric curves: Most extrapolations (Weibull, log-logistic, gamma, exponential) fail to capture the initial increase in hazards in the NIVO+IPI arm.
- Consistency with the types of models chosen for other portions of the model for TTP, including models fit to data after the MAIC: These choices were also in line with what was recommended in NICE DSU Technical Support Document (TSD) 14,[66] which recommends fitting the same type of model for each treatment arm when parametric models are fitted separately to individual treatment arms.

Therefore, utilisation of the generalised gamma model for NIVO+IPI is in line with best practice, particularly as the parametric alternatives considered (log-normal and log-logistic) did not perform significantly better in terms of fit statistics or adherence to the shape of the observed data. Furthermore, the generalised gamma model was validated against the best-fitting standard parametric fit to CM 142 NIVO monotherapy data through 5 years, and its values were found to be clinically plausible.

Figure 26. Standard parametric fits of the PF-to-PD transition ($p_{1,2}$) for the CM 8HW NIVO+IPI arm, extrapolated beyond the observed trial period

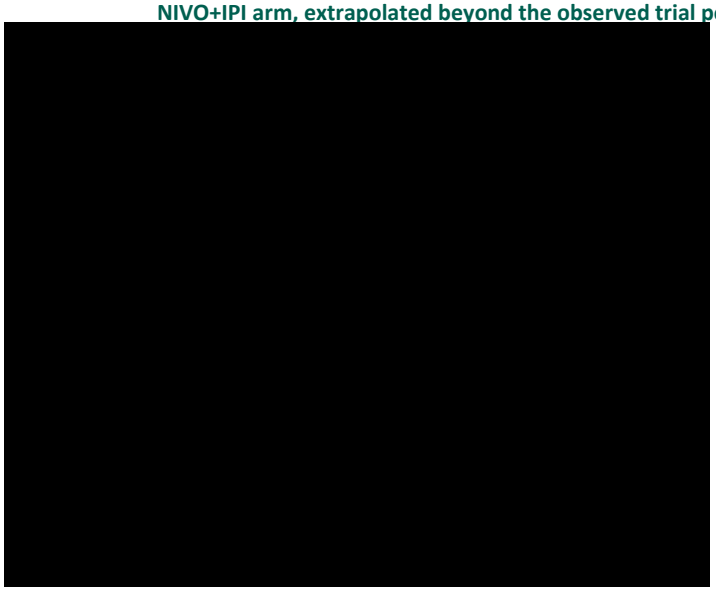


Table 25 summarises the assumptions associated with extrapolation for NIVO+IPI.

Table 25. Summary of assumptions associated with extrapolation of TTP for NIVO+IPI

Method/approach	Description/assumption
Data input	CM 8HW
Model	Standard parametric survival model
Assumption of proportional hazards between intervention and comparator	Violated
Function with best AIC fit	Generalised gamma
Function with best BIC fit	Generalised gamma
Function with best visual fit	Generalised gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Generalised gamma
Validation of selected extrapolated curves (external evidence)	NIVO+IPI compared with NIVO monotherapy arm in the CM 142 trial (see Appendix D)
Function with the best fit according to external evidence	When validated against the CM 142 NIVO arm, generalised gamma was considered the best-fitting function
Selected parametric function in base-case analysis	Generalised gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/crossover	No
Assumptions of waning effect	No
Assumptions of cure point	No

Extrapolation of PF-to-PD transition for PEMBRO

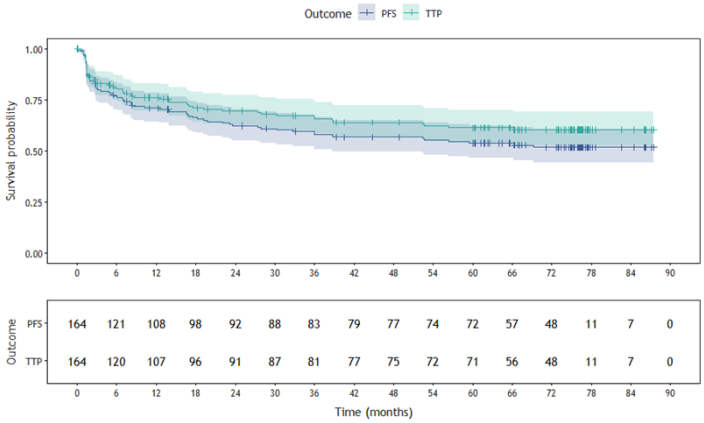
As presented in Section 7, an MAIC was performed comparing PFS for PEMBRO with NIVO+IPI using aggregate data from KN-177 and IPD from CM 8HW, producing re-weighted CM 8HW data that were used to estimate the PF-to-PD transition for the PEMBRO arm.

Based on the model structure, the ITC would ideally compare the TTP between NIVO+IPI and PEMBRO. However, only PFS data are published and available from KN-177 (i.e., including patients that progress as well as die). To enable a comparison of similar data across trials, the ITC estimated the comparative efficacy for the outcome PFS of NIVO+

IPI versus PEMBRO. This approach assumed that the HR between treatments of PFS was comparable to the HR of TTP. This assumption was deemed acceptable because:

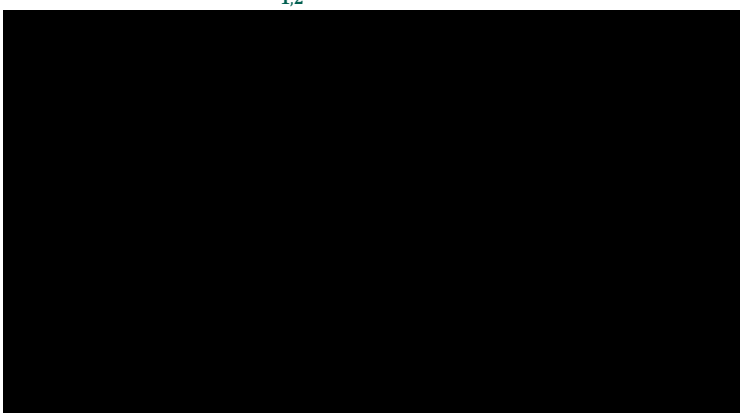
- The phase 2 CM 142 study indicates most PFS events were progressions (see KM curves comparing PFS and TTP in the NIVO+IPI cohorts in Figure 27).
- The trial populations are relatively young (median age, 63 years).

Figure 27. Comparison of PFS and TTP for cohort 2+3 (NIVO+IPI) in CM 142



Based on the results from the ITC (see Section 7) and the TTP survival extrapolation of NIVO+IPI, Figure 28 presents the predicted base-case PF-to-PD ($p_{1,2}$) survival for NIVO+IPI and PEMBRO.

Figure 28. PF-to-PD ($p_{1,2}$) survival for NIVO+IPI and PEMBRO



8.1.1.2 Extrapolation of PD-to-Death transition ($p_{2,3}$) based on unmatched CM 142 data

As CM 8HW OS data were unavailable, CM 142 data were used to estimate the transition from PD to Death ($p_{2,3}$). The KN-177 OS data also were unavailable. It is assumed that postprogression survival between the NIVO+IPI arm and PEMBRO arm is equal.

An exploratory matching analysis was carried out to determine if CM 142 data could be matched to CM 8HW to make the populations more similar (Appendix D). The matching analysis resulted in a small ESS due to weighting (ESS is n = 17 in the matched CM 142 data versus n = 164 in the unmatched CM 142 population), and it was found that the KM curves produced by the matched CM 142 data were comparable to the unmatched CM

142 data as the 95% CIs of both overlapped. Moreover, the median survival of the matched CM 142 was equal to that of the unmatched one (15.9 months). However, there was more uncertainty associated with the estimates of transitions from PD to Death. This is likely due to the large reduction in sample size caused by matching, which could be driven by differences in study design and patient characteristics. Based on the result of the analysis, it concluded that the unmatched CM 142 data would be used to estimate the PD-to-Death transition ($p_{2,3}$) in the base case (Figure 29).

For the unmatched CM 142 data, 57 patients were included in this transition, all of whom received NIVO+IPI (cohorts 2 and 3). This included patients in CM 142 who died after being diagnosed with progressed disease. The median time to death after experiencing progressed disease was 15.9 months (95% CI, 11.8-37.1 months), and the 1-year death-free probability after experiencing progressed disease was 0.61 (95% CI, 0.50-0.75). Table 26 summarises the assumptions associated with extrapolation of the PD-to-Death transition ($p_{2,3}$) based on unmatched CM 142 data. Of the models fit, the Gompertz and exponential models were excluded straightaway due to poor fit or implausible extrapolations. Of the remaining candidate models, the three with the lowest AIC values were log-logistic, Weibull, and gamma; among these, the log-logistic had the most optimistic extrapolations but lowest median PFS (18.5 months), which was closest to the observed median of 15.8 months (see Appendix D for details and figures). Therefore, the log-logistic model was chosen as the base-case PD-to-Death survival (Figure 29) for the economic model.

Figure 29. PD-to-Death ($p_{2,3}$) survival model for the base case

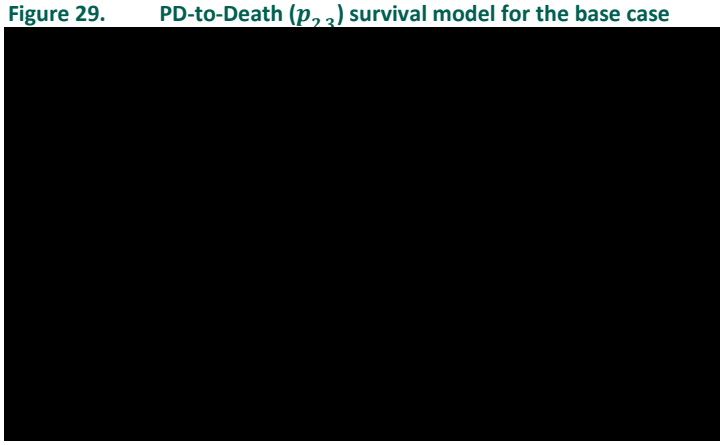


Table 26. Summary of assumptions associated with extrapolation of the PD-to-Death transition ($p_{2,3}$) based on unmatched CM 142 data

Method/approach	Description/assumption
Data input	CM 142
Model	Standard parametric survival model
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Gompertz

Method/approach	Description/assumption
Function with best BIC fit	Gompertz
Function with best visual fit	Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Log-logistic, Gompertz, and log-normal
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base-case analysis	Log-logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/crossover	No
Assumptions of waning effect	No
Assumptions of cure point	No

General population mortality data were used as the base-case scenario to estimate the transition probability from PF to Death ($p_{1,3}$). Clinical experts from an advisory board recommended using background mortality for this transition, as it is likely to accurately represent the PF-to-Death transition ($p_{1,3}$) in these patients. The PF-to-Death data ($p_{1,3}$) from the CM 142 trial were available, but the data were immature because only a limited number of events occurred during the trial period. Therefore, general population mortality was used in the base-case model. However, transition probabilities based on CM 142 have been included in the model as an option for estimating transition probabilities of the PF-to-Death transition ($p_{1,3}$) (see Appendix D for more information) and have been explored in the scenario analysis.

To estimate the transition probability from PF to Death ($p_{1,3}$), annual probabilities of mortality for the general population were obtained from the Danish life tables Statistics Denmark (2024)[69] from 2022-2023. 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:

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

8.1.2 Calculation of transition probabilities

As outlined in Section 4, a three-state semi-Markov model was developed using data from CM 8HW, CM 142, and KN-177 to estimate the cost-effectiveness of NIVO+IPI

versus PEMBRO (see Figure 3 for model structure). In this semi-Markov model, the cohort of patients moves through the three health states (i.e., Progression Free (PF), Progressed Disease (PD), and Death) according to a set of transition probabilities, also called a *transition probability matrix*.

The transition probability from PD to Death and the probability of remaining in PD depend on the time spent in the PD state. For PFS, time-varying estimates can be easily 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 PD is considerably more complex.

Therefore, in the model, such time-dependent probabilities have been implemented in a VBA macro for efficiency purposes. Transition probabilities are estimated in a separate Excel sheet for all transitions for all states for each treatment that are then loaded into the macro. In the macro, the health-state occupancy is then calculated using a three-dimensional array in which 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 PF, the time spent in the health state is equal to the model cycle length; therefore, including the sojourn time does not make a difference. However, for PD, 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*.

The estimation of transition probabilities for the PF-to-PD ($p_{1,2}$), PF-to-Death ($p_{1,3}$), and PD-to-Death ($p_{2,3}$) transitions encompassed transitions from all states required for the analysis. Additionally, the probability of a patient remaining in the same state was estimated as 1 – the probability of leaving each state.

Table 27 presents the assumptions for transition probabilities. Transitions from PF to PD ($p_{1,2}$) are estimated using individual patient data (IPD) from the clinical trial CM 8HW for NIVO+IPI and through a matching indirect treatment comparison (MAIC) using IPD from CM 8HW and aggregate data from KN-177 for PEMBRO. For the transitions from PF to Death ($p_{1,3}$), background mortality is used for both treatments. Individual patient data from CM 142 for the NIVO+IPI arm is used to estimate the transitions from PD to Death ($p_{2,3}$); these transitions are assumed equal for both treatments. Sections 7, 8.1, and Appendix D present more details on the clinical data used, the rationale and assumptions behind the choices of data, and the estimation and choice of transition probabilities in the model.

Table 27. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Progression Free	Progressed Disease	Estimated using IPD from clinical trials (CM 8HW, CM 142) for NIVO+IPI. For PEMBRO, transition probabilities were estimated through an MAIC using IPD from CM 8HW and aggregate data from KN-177. A time-varying HR for the PEMBRO vs. NIVO+IPI comparison was included in the base case. The probability of a patient remaining in the same state was estimated as 1 – the probability of leaving each state	CM 8HW[10] CM 142[47] KN-177[39]
	Death	Estimated based solely on age-specific background mortality and used for all treatment arms.	Danish lifetable[69]
Progressed Disease	Death	IPD from CM 142 for the NIVO+IPI arm is used to estimate the transitions from Progressed Disease to Death, and these transitions are assumed equal for all treatments. The probability of a patient remaining in the same state was estimated as 1 – the probability of leaving each state	CM 142[47]

Figure 30 and Figure 31 show the proportion of patients in each health state per cycle for the NIVO+IPI and PEMBRO arms, respectively.

Figure 30. Proportion of patients in each health state per cycle for NIVO+IPI

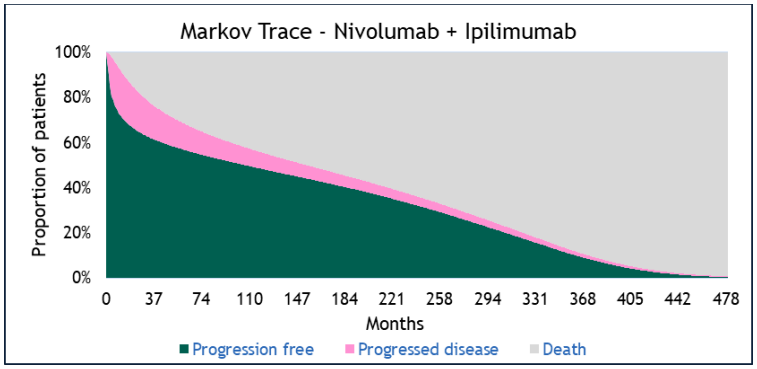
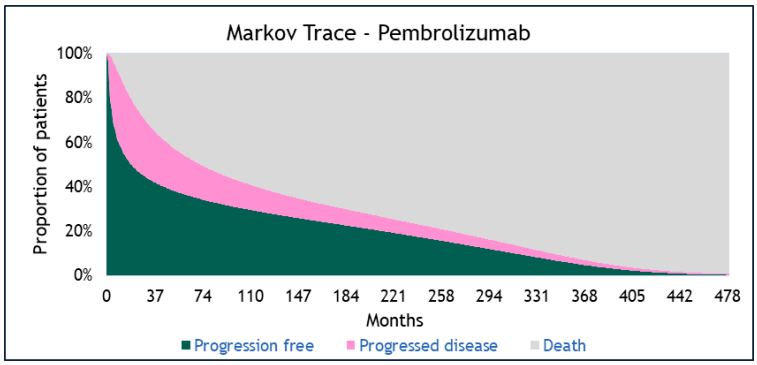


Figure 31. Proportion of patients in each health state per cycle for PEMBRO



8.2 Presentation of efficacy data from additional documentation

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable, as postprogression survival is assumed to be equal for both treatments.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

In CM 8HW, among NIVO+IPI patients, the median PFS (in months) was not reached. Table 28 presents modelled average and modelled median PFS predicted by the economic model as well as the observed median PFS from KN-177.

Table 28. Estimates of PFS in the model

	Modelled average PFS (reference in Excel)	Modelled median PFS (reference in Excel)	Observed median from relevant study
NIVO+IPI	150.4 months	106.7 months	Not reached
PEMBRO	92.2 months	18.4 months	16.5 (95% CI, 5.4-32.4) months

Treatment duration is based on the mean doses received for NIVO+IPI in CM 8HW. For PEMBRO, the median time on treatment is from KN-177 and is assumed to be representative of the mean duration. As such, this has been included only as point of reference but is not explicitly modelled as a “health state” in the model. Table 29 provides the modelled average treatment length and time in model health state.

Table 29. **Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half-cycle correction**

Treatment	Treatment length (months)	Time in health state (months)	
		Progression Free	Progressed Disease
NIVO+IPI	13.26	150.4	26.1
PEMBRO	11.1	92.2	38.3

9 Safety

9.1 Safety data from the clinical documentation

In CM 8HW, 200 participants in the NIVO+IPI arm and 88 in the chemotherapy arm received at least one dose of the study drug and therefore were included in the safety analysis.[10] In first-line treated participants, NIVO+IPI had a favourable safety profile compared with chemotherapy despite a longer median treatment duration [redacted] There were two treatment-related deaths in the NIVO+IPI arm.[43] The most common adverse reaction was pruritus in the NIVO+IPI arm, whereas diarrhoea was the most common in the chemotherapy arm. Other common adverse reactions in both arms were asthenia, decreased appetite, and nausea.

In KN-177, 153 participants in the PEMBRO arm and 143 in the chemotherapy arm were included in the safety analysis, which included all participants who underwent randomisation and received at least one dose of trial medication. Participants who received PEMBRO had a favourable safety profile compared with chemotherapy, despite a longer median treatment duration (11.1 months [range, 0.0-30.6] vs. 5.7 months [range, 0.1-39.6]).[39]

Table 30 presents AEs (all-causality AEs) and adverse reactions (treatment-related AEs) for both CM 8HW and KN-177. [redacted][10,39]

In Section 9.1, data on the serious AEs (SAEs) for NIVO+IPI requested by DMC are presented. However, equivalent data for PEMBRO are not publicly available; therefore, the data for PEMBRO are presented separately in Section 9.1. It is important to note that the KN-177 data are for grade 3-5 AEs and therefore should not be compared with the SAEs from CM 8HW. Within Section 9.1, we also present the immune-mediated AEs (IMAEs) for both regimens; again, data are not available in the same format so should not be directly compared.

Table 30. CM 8HW and KN-177: overview of safety events (all-treated population: median study follow-up of 31.51 months in CM 8HW and 32.4 months in KN-177)

	NIVO+IPI (n = 200)	Chemo (n = 88)	Difference, % (95% CI)	PEMBRO (n = 153)	Chemo (n = 143)	Difference, % (95% CI)
Number of AEs, n						
Number and proportion of participants with ≥ 1 AE, n (%)	[redacted]	[redacted]	[redacted]	149 (97.4)	142 (99.3)	−1.9 (−4.8 to 0.9)
Number of SAEs,[a] n						
Number and proportion of participants with ≥ 1 SAE,[b] n (%)	[redacted]	[redacted]	[redacted]	25 (16.3)	41 (28.7)	−12.3 (−23.0 to −1.6)
Number of CTCAE grade ≥ 3 events,[c] n						
Number and proportion of participants with ≥ 1 CTCAE grade ≥ 3 event, n (%)	[redacted]	[redacted]	[redacted]	33 (21.6)	95 (66.4)	−44.9 (−56.2 to −33.5)
Number of adverse reactions, n						
Number and proportion of participants with ≥ 1 adverse reaction, n (%)	[redacted]	[redacted]	[redacted]	NR	NR	NR
Number and proportion of participants who had a dose delay or dose reduction, n (%)	[redacted]	[redacted]	[redacted]	NR	NR	NR
Number and proportion of participants who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]	[redacted]	NR	NR	NR
Number and proportion of participants who discontinue treatment due to AEs, n (%)	[redacted]	[redacted]	[redacted]	21 (13.7)	17 (11.9)	1.8 (−6.4 to 10.1)

[a] AEs are defined as all-causality AEs. [b] An SAE is an event or reaction that, at any dose, results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). [c] CTCAE v. 5.0. Sources: BMS data on file (2024)[10]; Diaz et al. (2022)[45]; Andre et al. (2020)[39]

Table 31 summarises classes of SAEs with a frequency of ≥ 5% in participants within 30 days of last dose in any study arm of CM 8HW (all-treated population, median study follow-up of 31.51 months). [redacted][10] Data are available only on the number of patients with SAEs and not the number of SAEs. Appendix E provides information about all SAEs observed in CM 8HW.

Table 31. Serious adverse events

	No. (%) of participants with AEs	
SAE[a]	NIVO+IPI (n = 200)	Chemo (n = 88)
Total participants with an event	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Injury, poisoning, and procedural complications	[redacted]	[redacted]

Note: Data on the number of SAEs experienced are not available [a] An SAE is an event or reaction that, at any dose, results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). Source: BMS data on file (2024)[10]

Information on the AEs in CM 8HW are reported in Table 32.[56] These are grade 3-5 AEs and not SAEs and therefore can be compared with the KN-177 data presented in Table 34. Only 4 adverse reactions of grade 3-5 in ≥5% of participants were reported, and these were all in the chemo arm.

Table 32. CM 8HW: adverse reactions grade 3-5 in ≥ 5% of participants in any treatment arm (all-treated population)

	NIVO+IPI (n = 200)	Chemo (n = 88)
Experienced ≥ 1 grade 3-5 AE, n (%)		
Asthenia	[redacted]	[redacted]

	NIVO+IPI (n = 200)	Chemo (n = 88)
Neutrophil count decreased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Source: DMC (2021)[37],BMS data on file (2024)[56] ENREF 37

[redacted] (Table 33).[10]

Table 33. CM 8HW: IMAEs in ≥ 1% of all randomly assigned participants in any treatment arm (all-treated population)

	NIVO+IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Non-endocrine IMAEs within 100 days of last dose treated with immune-modulating medication, by category, n (%)[a]				
Diarrhoea/colitis	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis/renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity/infusion reactions	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine IMAEs within 100 days of last dose with or without immune-modulating medication, by category, n (%)[a]				
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism/thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Any OESIs within 100 days of last dose with or without immune-modulating medication, by category, n (%)[a,b]				
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]
Encephalitis	[redacted]	[redacted]	[redacted]	[redacted]
Myositis/rhabdomyolysis	[redacted]	[redacted]	[redacted]	[redacted]
Myasthenic syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]	[redacted]	[redacted]

[a] MedDRA version 26.1; CTC version 5.0. Includes events reported between first dose and 30 days after last dose of treatment, unless otherwise indicated. Excludes data collected on or after first crossover date. [b] No OESIs were reported in the following categories: demyelination, Guillain-Barré syndrome, uveitis, and graft-vs-host disease. Source: BMS data on file (2024)[10]

Information on the AEs in KN-177 is taken from the DMC appendix for the PEMBRO appraisal.[37] These are grade 3-5 AEs and not SAEs and therefore cannot be compared with the CM 8HW data presented above. We have not identified published data on the SAEs in KN-177. The most common adverse reaction was diarrhoea in both the PEMBRO and chemotherapy arms of KN-177. Other common adverse reactions in both arms were fatigue, nausea, abdominal pain, decreased appetite, and vomiting. Table 34 summarises the grade 3-5 adverse reactions that occurred in ≥ 5% of participants in either the PEMBRO or chemotherapy arms.

Table 34. KN-177: adverse reactions grade 3-5 in ≥ 5% of participants in any treatment arm (all-treated population)

	PEMBRO (n = 153)	Chemo (n = 143)
Experienced ≥ 1 grade 3-5 AE, n (%)	86 (56.2)	111 (77.6)
Hypertension	11 (7.2)	7 (4.9)
Diarrhoea	9 (5.9)	16 (11.2)
Abdominal pain	8 (5.2)	8 (5.6)
Anaemia	8 (5.2)	15 (10.5)
Hyponatraemia	8 (5.2)	4 (2.8)
Hypokalaemia	2 (1.3)	9 (6.3)
Neutropenia	0 (0)	22 (15.4)
Neutrophil count decreased	0 (0)	24 (16.8)

Source: DMC (2021)[37]

Immune-mediated AEs were also reported for KN-177, but reporting was not consistent between the two trials; therefore, comparison is inappropriate. As anticipated, IMAEs occurred more frequently in the PEMBRO arm than in the chemotherapy arm (Table 35).

Table 35. KN-177: IMAEs and infusion reactions in the all-treated population

	PEMBRO (n = 153)		Chemo (n = 143)	
Event, n (%)	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any AE of interest	47 (31)	14 (9)	18 (13)	3 (2)
Hypothyroidism	19 (12)	0	3 (2)	0
Colitis	10 (7)	5 (3)	0	0
Hyperthyroidism	6 (4)	0	0	0
Pneumonitis	6 (4)	0	1 (1)	0

Event, n (%)	PEMBRO (n = 153)		Chemo (n = 143)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Adrenal insufficiency	4 (3)	2 (1)	0	0
Hepatitis	4 (3)	4 (3)	0	0
Infusion reactions	3 (2)	0	11 (8)	1 (1)
Severe skin reactions	2 (1)	2 (1)	2 (1)	2 (1)
Thyroiditis	2 (1)	0	0	0
Hypophysitis	2 (1)	0	0	0
Myocarditis	0	0	1 (1)	0
Nephritis	1 (1)	0	0	0
Pancreatitis	1 (1)	1 (1)	0	0
Type 1 diabetes	1 (1)	1 (1)	0	0
Myositis	1 (1)	0	0	0

Note: AEs of interest were IMAEs and infusion reactions, derived from a list of terms specified by the sponsor, regardless of attribution to any trial treatment by investigators. Source: Andre et al. (2020)[39]

9.1.1 Safety data from the trials used in the economic model

For the cost-effectiveness base case, the incidence of AEs was used to estimate treatment-specific disutilities and costs of AEs. Treatment-emergent AEs were included in the model according to the following inclusion criteria:

- Non-endocrine events: diarrhoea/colitis, hepatitis, rash, and pneumonitis
- Endocrine events: adrenal insufficiency, hyperthyroidism, and hypophysitis
- Grade ≥ 3 AEs in severity with an incidence of ≥ 5% presented in the respective clinical trials for all treatments included in the model

Some additional specific adverse events (neutropenia, asthenia, decreased neutrophil count and hypertension) were included as it was considered that they may impact costs and outcomes. The incidence of AEs included per treatment arm was based on all AEs reported in CM 8HW for NIVO+IPI and KN-177 for PEMBRO (Table 36).

Table 36. AEs used in the health economic model

AEs (%)	NIVO+IPI	PEMBRO
Hepatitis	[redacted]	2.6
Neutropenia	[redacted]	0.7
Rash	[redacted]	1.3
Diarrhoea/colitis	[redacted]	3.3
Adrenal insufficiency	[redacted]	1.3
Hyperthyroidism	[redacted]	NR
Hypophysitis	[redacted]	NR
Asthenia	[redacted]	2.0
Decreased neutrophil count	[redacted]	NR
Hypertension	[redacted]	7.2
Pneumonia	[redacted]	3.3

Source: BMS data on file (2024)[70]

9.2 Safety data from external literature applied in the health economic model

The incidence of AEs for PEMBRO in the economic model were taken from TA709[63] and Andre et al. (2020)[39]. The incidence has been presented in Table 34 and Table 36. No other external literature has been used; therefore, the template table "AEs that appear in more than X % of patients" has not been completed.

10 Documentation of health-related quality of life (HRQoL)

In both CM 8HW and KN-177, EORTC QLQ-C30 and EQ-5D-3L data were collected (Table 37).

Table 37. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L	CM 8HW, KN-177	Clinical effectiveness, utility estimates

Measuring instrument	Source	Utilization
EORTC QLQ-C30	CM 8HW, KN-177	Clinical effectiveness

10.1 Presentation of the health-related quality of life

For CM 8HW, EORTC QLQ-C30 results are available only for the participants with centrally confirmed dMMR/MSI-H, while EQ-5D-3L results are available for all participants (i.e., locally confirmed). For KN-177, results of both EORTC QLQ-C30 and EQ-5D-3L are available only for participants with locally confirmed dMMR/MSI-H.

No ITC was conducted for HRQoL results, hence the presented results are for NIVO+IPI compared with investigator's choice chemotherapy[71] and PEMBRO compared with investigator's choice chemotherapy[72] from the respective studies.

For EORTC QLQ-C30, GHS/QoL scores are presented; for the EQ-5D-3L, visual analogue scale (VAS) scores and health utility index scores are presented.

10.1.1 Study design and measuring instrument

CM 8HW (NCT04008030) is a phase 3, randomised, open-label study, and KN-177 (NCT02563002) was a phase 3, randomised, open-label study (see Section 6 for details for both studies). Table 38 presents the validity, reliability, and sensitivity of EORTC QLQ-C30 GHS/QoL scores and the EQ-5D-3L for the patient population applicable in this assessment. In CM 8HW, there were no prior expectations of change in HRQoL. These outcomes were exploratory, and the trial was not powered to test any hypotheses related to these exploratory analyses; *P* values are considered descriptive only (using nominal $\alpha = 0.05$). The instruments were used in the manner for which they have been validated, and the study design and chosen instruments are not anticipated to create any particular risk of bias.

Table 38. Validity, reliability, and sensitivity of EORTC QLQ-C30 GHS/QoL scores and the EQ-5D-3L

Endpoint measure and source	Validity, reliability, and sensitivity
HRQoL BMS data on file (2024)[71]; Andre et al. (2021)[72]	The EORTC QLQ-C30 is the most commonly used QoL instrument in trials in mCRC. A significant change in EORTC QLQ-C30 scores can be interpreted as small, moderate, or large changes in QoL as reported by patients in a subjective significance questionnaire.[73] For patients with little change, the mean change in scores is approximately 5-10, with 10 being *moderate* and 20 being *very much* in bladder oncology trials.[74] EQ-5D-3L is a standard, generic, self-report survey used in clinical trials to measure QoL and preferred by HTA bodies for subsequent estimates of utility.

10.1.2 Data collection

10.1.2.1 CM 8HW: NIVO+IPI

Table 39 presents an overview of the data collection; Table 40 and Table 41 provide more detailed information including missing data for EORTC QLQ-C30 and EQ-5D-3L. Clinical outcome assessments (COAs) were administered before day 1 of each treatment cycle for cycles 1 to 3 (cycles 1 and 2 = 6 weeks; cycle 3 = 4 weeks) and then every other cycle (every 8 weeks) thereafter. During follow-up, COAs were administered during safety follow-up visits 1 and 2 (all COAs) and survival follow-up visits every 3 months (EQ-5D-3L only).[71] The results reported below are based on a November 2023 database lock when the median follow-up was [redacted] [71]

The known reasons for missing clinical outcome assessment data at each timepoint in the treatment period were presented, based on the known disposition of the participants and the planned study design (i.e., died, progressed, discontinued treatment, terminated the study). The clinical outcome assessment data were planned to be collected while participants were on treatment and then at follow-up visits. Per protocol, participants received treatment until progression, toxicity, discontinuation for other reasons, or reaching maximum treatment duration.[71]

When considering the patient-reported outcome (PRO) instrument completion numbers at the baseline/postbaseline level, the overall proportion of participants with any PRO data was high at [redacted] but was notably [redacted] in the NIVO+IPI group ([redacted]) compared with chemotherapy ([redacted]). This difference in completion rates between the groups is due to nine participants randomly assigned to chemotherapy who were not treated and thus did not complete the baseline assessment or any postbaseline assessments. There was also a much [redacted] of chemotherapy participants ([redacted]) with baseline-only EORTC QLQ-C30 data compared with the NIVO+IPI arm ([redacted]). Additionally, [redacted] of participants had baseline and postbaseline EORTC QLQ-C30 assessments in the NIVO+IPI group, [redacted] had these assessments in the chemotherapy group, which was driven by rapid disease progression in the chemotherapy arm. The completion rates were broadly the same across instruments (Appendix F).[71]

Table 39. Overview of data collection with EORTC QLQ-C30 and the EQ-5D-3L

Outcome measure	Timepoint[a]	Definition	How was the measure investigated/method of data collection
HRQoL BMS data on file (2023)[38]; BMS data on file (2024)[71]	Longitudinal throughout treatment and follow-up at 30 and 100 days after last dose	EORTC QLQ-C30 GHS score; EQ-5D-3L score	Changes from baseline in HRQoL were measured using the EORTC QLQ-C30 version 3 GHS/QoL score and EQ-5D-3L. EQ-5D-3L was also measured in the treatment period and during follow-up visits.

[a] Timepoint for data collection used in analysis (follow-up time for time-to-event measures).

Table 40. Pattern of missing data and completion for EORTC QLQ-C30, randomly assigned first-line population with centrally confirmed dMMR/MSI-H status

	NIVO+IPI				Chemotherapy			
	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	NIVO+IPI				Chemotherapy			
	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
Week 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 77	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 101	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 117	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 125	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	NIVO+IPI				Chemotherapy			
	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
Week 141	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 149	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 165	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 173	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

dMMR/MSI-H = mismatch repair deficient/microsatellite instability-high; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Quality of Life of Cancer Patients (Core); HRQoL = health-related quality of life; IPI = ipilimumab; NIVO = nivolumab.

Source: BMS data on file (2024)[71]

Table 41. Pattern of missing data and completion for EQ-5D-3L, randomly assigned first-line population with locally confirmed dMMR/MSI-H status

	NIVO+IPI				Chemotherapy			
	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)	No. at randomisation	No. for whom data are missing (% of no.at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 53	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	NIVO+IPI				Chemotherapy			
	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)	No. at randomisation	No. for whom data are missing (% of no.at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
Week 61	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 77	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 101	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 109	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 117	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 125	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 133	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	NIVO+IPI				Chemotherapy			
	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)	No. at randomisation	No. for whom data are missing (% of no.at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
Week 141	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 149	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 157	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 165	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 173	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 181	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	NIVO+IPI				Chemotherapy			
	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)	No. at randomisation	No. for whom data are missing (% of no.at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
Survival follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	NIVO+IPI				Chemotherapy			
	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)	No. at randomisation	No. for whom data are missing (% of no.at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
Survival follow-up 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival follow-up 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

dMMR/MSI-H = mismatch repair deficient/microsatellite instability-high; HRQoL = health-related quality of life; IPI = ipilimumab; NA = not available; NIVO = nivolumab.

Source: BMS data on file (2024)[75]

[redacted] of NIVO+IPI participants and [redacted] of chemotherapy participants. [redacted] of NIVO+IPI participants and [redacted] of chemotherapy participants [redacted] There were [redacted] on chemotherapy and [redacted] on NIVO+IPI who had no completed assessments. Of these, [redacted]

The reason for missing on-treatment expected data was generally unknown. Missing on-treatment expected data were typically comparable between treatments, with neither treatment group showing consistently higher or lower expected missing data rates during the study period. For missing data that were not expected, the most common reasons for missing data in the NIVO+IPI group were treatment discontinuation due to [redacted] and [redacted] at week 21. In the chemotherapy group, the most common reasons were treatment discontinuation due to [redacted] and [redacted] at week 21. These patterns of results remained similar at later timepoints.[71]

[redacted]

Multiple imputation and joint modelling sensitivity analyses were conducted for the PRO scales [redacted] Table 42 summarises the estimates of the treatment differences at week 21 for the multiple imputation analysis and original cLDA mixed model repeated measures (MMRM) models. This shows that the estimated treatment effects from the multiple imputation analysis were [redacted]

Table 42. Longitudinal sensitivity analysis: comparison of original model (MMRM cLDA) with multiple imputation and joint shared parameter model in the EORTC QLQ-C30—week 21 treatment difference

		Difference (week 21) NIVO+IPI – chemotherapy, LSM (95% CI)			Association (95% CI)
Instrument/ scale	MID	cLDA MMRM	Sensitivity analysis: multiple imputation	Sensitivity analysis: continuous time model	Joint model
GHS/QoL						

Source: BMS data on file (2024)[71]

10.1.2.2 KN-177 - PEMBRO

Table 43 presents an overview of the data collection; Table 44, Table 45 and Table 46 presents a more detailed presentation including missing data. Questionnaires were administered at baseline and at weeks 2 (chemotherapy) or 3 (PEMBRO); followed by weeks 6, 9, 12, and 18; then every 9 weeks for up to 1 year or until the end of treatment; and at 30 days after treatment discontinuation. Patients who were expected to complete the HRQoL assessment did not include those missing by design because of death, discontinuation, or unavailability of translation of questionnaires. Missing data were treated as missing at random in the analysis.[72] We were unable to identify any further detail in the public domain. The median follow-time was reported as the time from randomisation to data cutoff, which was 32.4 months (IQR 27.7-37.8).[72]

Table 43. Overview of data collection with EORTC QLQ-C30 and the EQ-5D-3L

Outcome measure	Timepoint[a]	Definition	How was the measure investigated/method of data collection
HRQoL Andre et al. (2021)[72]	Longitudinal throughout treatment and follow-up at week 18	EORTC QLQ-C30 GHS score; EQ-5D-3L score	Changes from baseline in HRQoL were measured using the EORTC QLQ-C30 GHS/QoL score and EQ-5D-3L health utility and VAS score.

[a] Timepoint for data collection used in analysis (follow-up time for time-to-event measures). Source: Andre et al. (2021)[72]

Table 44. Pattern of missing data and completion for EORTC QLQ-C30, EQ-5D-3L VAS, and EQ-5D-3L health utility index score

	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. at randomisation	No. for whom data are missing (% of no. at randomisation)	No. "at risk" at timepoint X	No. who completed (% of no. expected to complete)
EORTC QLQ-C30				
Baseline	294	22 (7.5%)	292	272 (93.2%)
Follow-up 1 (18 weeks)	294	110 (37.4%)	292	184 (63.0%)
EQ-5D-3L VAS and EQ-5D-3L health utility index score				
Baseline	294	19 (6.5%)	292	275 (94.2%)
Follow-up 1 (18 weeks)	294	110 (37.4%)	292	184 (63.0%)

Source: BMS data on file (2024)[71]

Table 45. Compliance and completion rates[a] for the EORTC QLQ-C30 by study visit

Timepoint	Category	Pembrolizumab N = 152	Chemotherapy N = 141
Baseline	Expected to complete, n	152	141
	Completed, n	141	131
	Compliance rate in those expected to complete, %	92·8	92·9
	Completion rate in total population, %	92·8	92·9
Week 2/3	Expected to complete, n	144	136
	Completed, n	132	125
	Compliance rate in those expected to complete, %	91·7	91·9
	Completion rate in total population, %	86·8	88·7
Week 6	Expected to complete, n	136	127
	Completed, n	126	102
	Compliance rate in those expected to complete, %	92·6	80·3

Timepoint	Category	Pembrolizumab N = 152	Chemotherapy N = 141
	Completion rate in total population, %	82·9	72·3
Week 9	Expected to complete, n	128	118
	Completed, n	119	58
	Compliance rate in those expected to complete, %	93·0	49·2
	Completion rate in total population, %	78·3	41·1
Week 12	Expected to complete, n	124	119
	Completed, n	114	88
	Compliance rate in those expected to complete, %	91·9	73·9
	Completion rate in total population, %	75·0	62·4
Week 18	Expected to complete, n	116	107
	Completed, n	102	82
	Compliance rate in those expected to complete, %	87·9	76·6
	Completion rate in total population, %	67·1	58·2
Week 27	Expected to complete, n	106	81
	Completed, n	79	38
	Compliance rate in those expected to complete, %	74·5	46·9
	Completion rate in total population, %	52·0	27·0
Week 36	Expected to complete, n	100	66
	Completed, n	80	35
	Compliance rate in those expected to complete, %	80·0	53·0
	Completion rate in total population, %	52.6	24.8
Week 45	Expected to complete, n	86	50
	Completed, n	72	28
	Compliance rate in those expected to complete, %	83.7	56.0

Timepoint	Category	Pembrolizumab N = 152	Chemotherapy N = 141
	Completion rate in total population, %	47.4	19.9

[a] Compliance rate was defined as the number of patients who completed at least one item divided by the number of eligible patients who were expected to complete the HRQoL assessment (not including patients missing by design due to death, discontinuation, or translation not available). Completion rate was defined as the number of patients in the HRQoL analysis population who completed at least one item divided by the number of patients in the HRQoL analysis population (patients who received at least one dose of study medication and had completed at least one HRQoL assessment).

EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL, health-related quality of life.

Source: Andre et al. (2021)[72]

Table 46. Compliance and completion rates for the EQ-5D by study visit

Timepoint	Category	Pembrolizumab N = 152	Chemotherapy N = 142
Baseline	Completion, n (%)	142 (93)	133 (94)
	Compliance, n (%)	142/152 (93)	133/142 (94)
Week 2/3	Completion, n (%)	132 (87)	128 (90)
	Compliance, n (%)	132/144 (92)	128/137 (93)
Week 6	Completion, n (%)	126 (83)	102 (72)
	Compliance, n (%)	126/136 (93)	102/128 (80)
Week 9	Completion, n (%)	119 (78)	58 (41)
	Compliance, n (%)	119/128 (93)	58/119 (49)
Week 12	Completion, n (%)	114 (75)	89 (63)
	Compliance, n (%)	114/124 (92)	89/120 (74)
Week 18	Completion, n (%)	102 (67)	82 (58)
	Compliance, n (%)	102/116 (88)	82/108 (76)
Week 27	Completion, n (%)	79 (52)	39 (28)
	Compliance, n (%)	79/106 (75)	39/82 (48)
Week 36	Completion, n (%)	80 (53)	36 (25)
	Compliance, n (%)	80/100 (80)	36/67 (54)

Timepoint	Category	Pembrolizumab N = 152	Chemotherapy N = 142
Week 45	Completion, n (%)	72 (47)	28 (20)
	Compliance, n (%)	72/86 (84)	28/51 (55)

Compliance rate was defined as the number of patients who completed at least one item divided by the number of eligible patients who were expected to complete the HRQoL assessment (not including patients missing by design due to death, discontinuation, or translation not available). Completion rate was defined as the number of patients in the HRQoL analysis population who completed at least one item divided by the number of patients in the HRQoL analysis population (patients who received at least one dose of study medication and had completed at least one HRQoL assessment).

EQ-5D; EuroQoL 5 Dimensions; HRQoL, health-related quality of life

Source: Andre et al. (2021)[72]

10.1.3 HRQoL results

Because BMS does not have access to unpublished data for KN-177, an ITC comparing NIVO+IPI with PEMBRO has not been possible due to equivalent data not being publicly available, and outcomes between the two trials have been measured at different timepoints. Therefore, the results are presented in two separate subsections below. However, the results presented below show that NIVO+IPI and PEMBRO are both superior to chemotherapy in the respective trials.

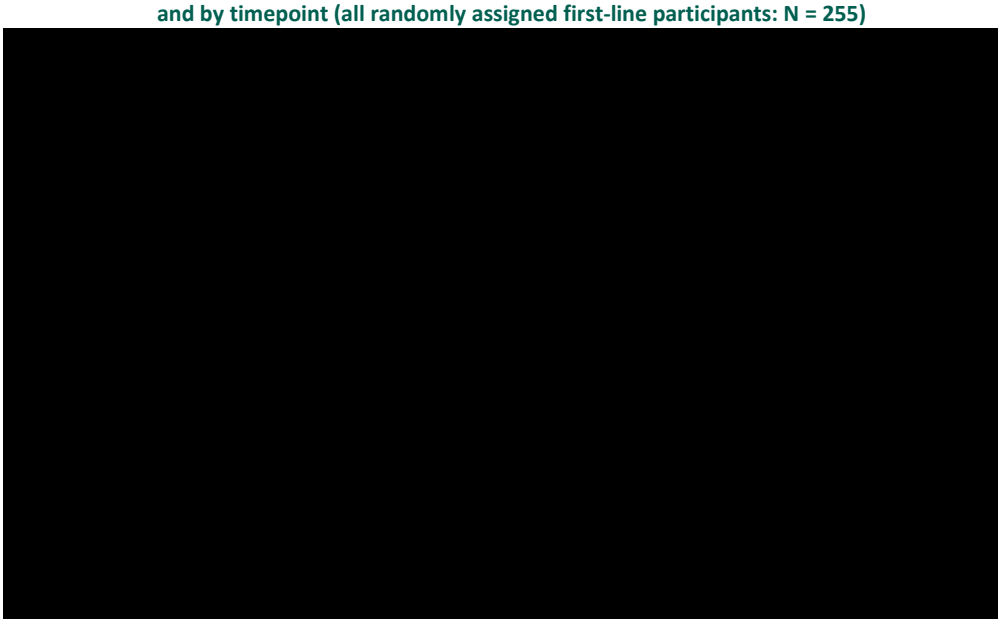
10.1.3.1 CM 8HW - NIVO+IPI

Figure 32, Figure 33, and Figure 34 present the results for NIVO+IPI compared with chemotherapy at week 21, measured by the EORTC QLQ-C30 and EQ-5D-3L VAS and utility index using UK preference weights.[71] HRQoL summary statistics are presented in Table 47.

Figure 32. EORTC QLQ-C30: change from baseline longitudinal analysis (MMRM) results overall and by timepoint (all randomly assigned first-line participants: N = 255)

Source: BMS data on file (2024)[71]

Figure 33. EQ-5D-3L VAS: change from baseline longitudinal analysis (MMRM) results overall and by timepoint (all randomly assigned first-line participants: N = 255)



Source: BMS data on file (2024)[71]

Figure 34. EQ-5D-3L utility index: change from baseline longitudinal analysis (MMRM) results overall and by timepoint (all randomly assigned first-line participants: N = 255)

Source: BMS data on file (2024)[71]

Table 47. HRQoL summary statistics: treatment difference at week 21

	NIVO+IPI		Chemo		NIVO+IPI vs. chemo	
	N	LSM (95% CI)	N	LSM (95% CI)	LSM (95% CI)	*P* value
GHS/QoL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

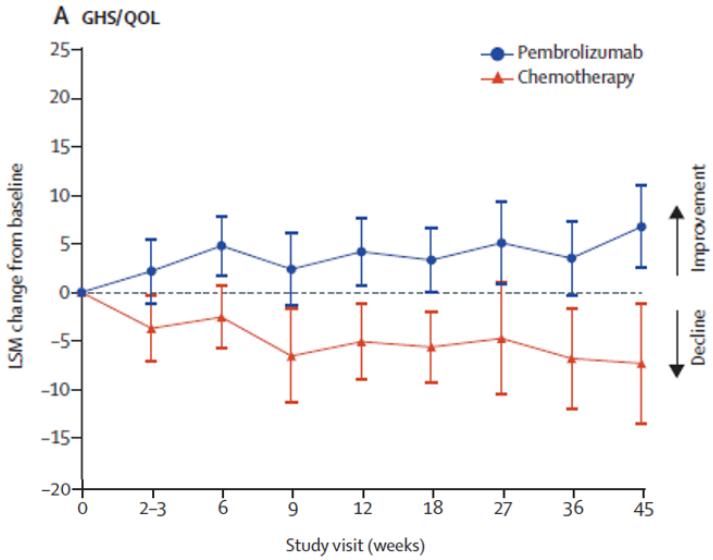
	NIVO+IPI		Chemo		NIVO+IPI vs. chemo	
	N	LSM (95% CI)	N	LSM (95% CI)	LSM (95% CI)	*P* value
EQ-5D-3L VAS	[redacted]					
EQ-5D-3L utility index	[redacted]					

Source: BMS data on file (2024)[71]

10.1.3.2 KN-177: PEMBRO

Figure 35 and Table 48 present the results for PEMBRO compared with chemotherapy change from baseline, measured by the EORTC QLQ-C30 and EQ-5D-3L VAS and utility index score using UK preference weights.[72] No further HRQoL data for KN-177 have been identified.

Figure 35. EORTC QLQ-C30: LSM change from baseline to week 18



Source: Andre et al. (2021)[72]

Table 48. HRQoL summary statistics: treatment difference change from baseline to week 18

	PEMBRO		Chemo		PEMBRO vs. chemo	
	N	LSM (95% CI)	N	LSM (95% CI)	LSM (95% CI)	*P* value
GHS/QoL	151	3.33 (−0.05 to 6.72)	141	−5.63 (−9.32 to −1.94)	8.96 (4.24-13.69)	0.0002
EQ-5D-3L VAS	151	4.50 (1.16-7.83)	141	−2.88 (−6.46 to 0.69)	7.38 (2.82-11.93)	0.0016

	PEMBRO		Chemo		PEMBRO vs. chemo	
	N	LSM (95% CI)	N	LSM (95% CI)	LSM (95% CI)	*P* value
EQ-5D-3L utility index	151	0.04 (0.00-0.08)	141	−0.01 (−0.05 to 0.02)	0.05 (0.00-0.10)	0.031

Source: Andre et al. (2021)[72]

10.2 Health state utility values used in the health economic model

10.2.1 HSUV calculation

Health-state utility values (HSUVs) for the locally confirmed population are obtained from CM 8HW in which patients completed the EQ-5D-3L questionnaire. The EQ-5D-3L is a descriptive system used to compute a utility index with scores ranging from −0.109 (worst imaginable health state) to 1 (best imaginable health state).

The analysis of the patient-level EQ-5D-3L data was undertaken by using the linear mixed modelling approach. Linear mixed models for repeated measures are a conventionally used method to account for these aspects when deriving the EQ-5D utility values for each health state.[76] Linear mixed models use observations considering the correlation between repeated measurements and provide the option to include fixed and random effect terms for time and interactions with baseline covariates.[77] For this reason, linear mixed models are often used to analyse EQ-5D-3L data given the longitudinal and hierarchical nature of data (level 1 being the repeated measures that are nested within level 2, the patient).

Although differences were observed between the NIVO+IPI and chemotherapy arms while patients were progression free, overall utility values per health state were used for the model because health-state occupation rather than treatment was seen as the most important factor and utility decrements from AEs were modelled separately. In line with DMC guidelines, an age adjustment of the utility values was performed to ensure that the relative level of utility values would decline at a rate consistent with the expected decline in HRQoL observed within the general Danish population. The adjustment index recommended by the DMC was used for this analysis.[7]

10.2.1.1 Mapping

In alignment with the DMC methods guide,[78] the EQ-5D-3L was mapped to the EQ-5D-5L and was applied for the Danish utility index values. The ordered logistic regression (including adjacent dimensions and a latent factor) approach using the van Hout and Shaw algorithm was used to predict EQ-5D-5L responses from EQ-5D-3L responses for each individual assessment as collected in the study (as per the preferred model in Table 2 in van Hout and Shaw (2021)[79]). The Danish EQ-5D-5L value set was then used to obtain the

predicted EQ-5D-5L utility score for each individual assessment (relating to the preferred model in Table 2 in Jensen et al. (2021)[80]). The predicted EQ-5D-5L index value obtained for each individual assessment was used to estimate the mean utility values within the health-state models.

10.2.2 Disutility calculation

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 PF state in the first model cycle.

In a previous submission, the ERG recommended limiting the duration of the AE to 7 days based on expert opinion.[81] It was considered reasonable by clinical experts that the severity of AEs would be reduced sufficiently after 1 week resulting in grade ½ AEs for which disutilities were not included in the model. Endocrine AEs (adrenal insufficiency, hyperthyroidism, hypophysitis) were the only exception. For these events, duration was considerably longer based on prior technology appraisals. Table 49 summarises the duration of AEs used in the model.

Evidence on disutilities of AEs in patients with mCRC is lacking. Therefore, for many disutilities, estimates were derived from studies in other types of cancer. However, most utility values have been used previously in NICE technology appraisals, and their use is suggested by the NICE ERG.

Table 49. Duration in model cycles per AE

AE	Duration (in model cycles)	Sources
Hepatitis	0.25	CM 214 CSR 8.7-3.2[82]
Neutropenia	0.25	CM 214 CSR 8.7-3.2[82]
Rash	0.25	CM 214 CSR 8.7-3.2[82]
Diarrhoea/ colitis	0.25	CM 214 CSR 8.7-3.2[82]
Adrenal insufficiency	0.25	CM 214 CSR 8.7-3.2[82]
Hyperthyroidism	3.8575	CM 214 CSR 8.7-3.2[82]
Hypophysitis	3.8575	CM 214 CSR 8.7-3.2[82]
Asthenia	3.8575	CM 214 CSR 8.7-3.2 [82]
Decreased neutrophil count	0.25	CM 214 CSR 8.7-3.2[82]
Hypertension	0.25	CM 214 CSR 8.7-3.2[82]
Increased lipase	0.25	CM 214 CSR 8.7-3.2[82]

AE	Duration (in model cycles)	Sources
Pneumonia	0.25	CM 214 CSR 8.7-3.2[82]

10.2.3 HSUV results

Table 50 summarises the utility values per health state and disutilities used in the model.

Table 50. Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression Free	[redacted]	EQ-5D-5L	DK	EQ-5D-3L collected in CM 8HW was mapped to EQ-5D-5L and was applied for the Danish utility index values. Utility based on 2,116 responses from 288 patients
Progressed Disease	[redacted]	EQ-5D-5L	DK	EQ-5D-3L collected in CM 8HW was mapped to EQ-5D-5L and was applied for the Danish utility index values. Utility based on 321 responses from 83 patients
AE disutilities				
Hepatitis	−0.2 [N/A]	N/A	N/A	Assumed equal to hypothyroidism/asthenia in Swinburn et al. (2010)[83]
Neutropenia	−0.0607 [N/A]	N/A	N/A	Freeman et al. (2014)[50], SCOT trial data[50]
Rash	−0.04 [N/A]	N/A	N/A	Assumed equal to stomatitis in Shabaruddin et al. (2013)[84]
Diarrhoea/ colitis	−0.09 [N/A]	N/A	N/A	Freeman et al. (2014)[50], SCOT trial data[50]
Adrenal insufficiency	−0.2 [N/A]	N/A	N/A	Assumed equal to hypophysitis in Mai et al. (2021)[53]
Hyperthyroidism	−0.069 [N/A]	N/A	N/A	Assumed equal to hypertension in Doyle et al. (2008)[51]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Hypophysitis	−0.2 [N/A]	N/A	N/A	Assumed equal to hypothyroidism/asthenia in Swinburn et al. (2010)[83]
Asthenia	−0.08 [N/A]	N/A	N/A	Assumed same as fatigue in Freeman et al. (2014)[50], SCOT trial data[50]
Decreased neutrophil count	−0.0375 [N/A]	N/A	N/A	Freeman et al. (2014)[50], SCOT trial data [50]
Hypertension	−0.069 [N/A]	N/A	N/A	Doyle et al. (2008)[51]
Increased lipase	−0.08 [N/A]	N/A	N/A	Assumed same as anaemia in VEG105192 clinical study report (2010)[85]
Pneumonia	−0.195 [N/A]	N/A	N/A	Tolley et al. (2013)[52]

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

Not applicable

Table 51. Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A	N/A	N/A	N/A	N/A

11 Resource use and associated costs

11.1 Medicine – intervention and comparator

Drug acquisition costs for immunotherapies were obtained from the Danish Medicines Agency.[86] Table 52 reports the dosing schedule, relative dose intensity, administration frequency, and vial sharing per treatment. The costs per administration with or without vial sharing were estimated by identifying the units per administration by selecting the most optimal dose depending on the available formulation and multiplying this with the cost per unit (Table 53). The underlying assumption was that the cheapest formulation would be the preferred option. For the base case, vial sharing was assumed for all treatments.

In the model, administration frequency was based on the protocol, and the maximum treatment duration was based on the mean doses received (Table 54) for NIVO+IPI based on CM 8HW data. For PEMBRO, the median time on treatment from KN-177 was assumed to reflect the mean time on treatment and was used to calculate the mean doses received.

Table 52. Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Source
NIVO	3.0 mg/kg	100%	Q3W for four treatment cycles	Yes	OPDIVO SmPC (2024)[1]
NIVO	6.0 mg/kg	100%	Q4W after four treatment cycles	Yes	OPDIVO SmPC (2024)[1]
IPI	1 mg/kg	100%	Q3W for four treatment cycles	Yes	YERVOY SmPC (2024)[2]
PEMBRO	4.0 mg/kg	100%	Q6W	Yes	Keytruda SmPC (2024)[36]

Note: Patient weight (70.5 kg) used in the model (Table 14) is based on the average patient weight from CM 8HW.

Table 53. Drug acquisition costs for immunotherapies used in the model

Medicine	Citations	Dose per vial	Units per package	Cost per package(DKK)	Price per mg (DKK)
NIVO	Laegemiddlestyrelsen (Danish Medicines Agency) (2024)[87]; Laegemiddlestyrelsen (Danish Medicines Agency) (2024)[88]; Laegemiddlestyrelsen (Danish Medicines Agency) (2024)[89]	40.0 mg	1.00	3,431.27	85.78
		100.0 mg	1.00	8,523.80	85.24
		240.0 mg	1.00	20,457.13	85.24
IPI	Laegemiddlestyrelsen (Danish Medicines Agency) (2024)[90]; Laegemiddlestyrelsen (Danish Medicines Agency) (2024)[91]	50.0 mg	1.00	23,850.38	477.01
		200.0 mg	1.00	95,188.99	475.94
PEMBRO	Laegemiddlestyrelsen (Danish Medicines Agency) (2024)[92]	100.0 mg	1.00	21,573.58	215.74

Table 54. Mean doses received

Medicine	Mean doses received	Reference
NIVO+IPI induction	3.61	CM 8HW[10]
PEMBRO	16.09	Andre et al. (2020)[39]: median duration of treatment exposure in days/treatment cycle length
NIVO+IPI maintenance	11.90	CM 8HW[10]

The model incorporates the options to alternatively use the dosing as per the protocol and using time-on-treatment curves. For the scenario using the time-on-treatment curves, CM 8HW data are used for NIVO+IPI. For PEMBRO, time on treatment is assumed equal to PFS with a maximum duration of 2 years.

The table below includes the average treatment duration as requested. Please note that the mean duration of treatment from KN 177 is not publicly available to our knowledge. Consequently, the median duration, which is also provided in the submission, has been added to the table.

Trial arm and treatment	Mean duration (months)
CM 8 HW Nivo+ipi	
Nivo	[redacted]

Ipi	[redacted]
CM 8 HW Chemo	[redacted]
CM 8 HW Nivo mono	[redacted]
KN 177 Pembro	11.1 (Median)
KN 177 Chemo	5.7 (Median)

*From interim analysis 2 of CM 8HW based on a clinical data cutoff on 28 August 2024.

11.2 Medicine – co-administration

Not applicable.

11.3 Administration costs

All immunotherapies were administered intravenously. Unit costs for drug administration were obtained from the Danish Health Data Authority using diagnosis-related group (DRG) Tariffs (2024) (Table 55).

Table 55. Administration costs used in the model

Administration type	Unit cost (DKK)	DRG code	Reference
Intravenous	1,561	06MA98	Sundhedsdatastyrelsen (2024)[93]

11.4 Disease management costs

To obtain costs per model cycle for disease management/resource use, unit costs of resource use were multiplied with resource use per model cycle (Table 56). Unit costs were obtained from the Danish Health Data Authority using DRG Tariffs (2024), prior submission[7] for PEMBRO, or Rigshospitalets Labportal (2024)[94]. Resource use was obtained from a previous submission (Medicinrådet (2021)[7]) and adjusted for a 28-day cycle length.

Table 56. Disease management costs used in the model

Activity	Frequency per model cycle	Reference	Unit cost (DKK)	DRG code	Reference
Progressed-Free health state					
Liver function test	1.15	Medicinrådet (2021)[7]	73	-	Rigshospitalets Labportal (2024)[94]

Activity	Frequency per model cycle	Reference	Unit cost (DKK)	DRG code	Reference
CT scan	0.30	Medicinrådet (2021)[7]	2,021	30PR07	Sundhedsdatastyrelsen (2024)[93]
Consultation outpatient appointment (on treatment)	2.00	Medicinrådet (2021)[7]	1,561	06MA98	Sundhedsdatastyrelsen (2024)[93]
Consultation outpatient appointment (off treatment)	1.00				
Progressed Disease health state					
Progressed disease care: CT scan	0.17	Medicinrådet (2021)[7]	2,021	30PR07	Sundhedsdatastyrelsen (2024)[93]
Progressed disease care: consultation outpatient appointment	0.17	Medicinrådet (2021)[7]	1,561	06MA98	Sundhedsdatastyrelsen (2024)[93]

11.5 Costs associated with management of adverse events

Unit costs per AE were derived from the Danish Health Data Authority using DRG Tariffs (2024) (Table 57). To obtain costs per AE, unit costs per AE were multiplied with the incidence of the event and were incurred in the first model cycle.

Table 57. Costs associated with management of AEs

	Diagnose kode/DRG code	Unit cost (DKK)/DRG tariff	Source
Hepatitis	(DB159A)Hepatitis A UNS /07MA98	1,947.00 (MDC07 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Neutropenia	A (DD709)Neutropeni UNS/16MA98	2,111.00 (MDC16 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]

	Diagnose kode/DRG code	Unit cost (DKK)/DRG tariff	Source
Rash	A (DR219)Hudu dslæt UNS/09MA98	1,625.00 (MDC09 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Diarrhoea/ colitis	A (DK519)Ul-cerøs colitis UNS/06MA98	1,561.00 (MDC06 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Adrenal insuffi-ciency	A (DE274A)Biny rebarkinsuffi-ciens UNS /10MA98	1,847.00 (MDC10 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Hyperthyroidism	A (DE039)Hy-pothyroid-isme UNS /10MA98	1,847.00 (MDC10 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Hypophysitis	A (DE229)Øget hypofyseaktivi tet UNS /10MA98	1,847.00 (MDC10 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Asthenia	A (DR688A9B1) Funktionel lidelse, almen/træthe d/23MA03	5,103.00 (MDC23 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Decreased neutro-phil count	A (DD709)Neu-tropeni UNS/16MA98	2,111.00 (MDC16 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Hypertension	A (DC189)Kræft i tyktarmen UNS/06MA98	1,561.00 (MDC06 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]
Increased lipase	A (DC189)Kræft i tyktarmen UNS/06MA98	1,561.00 (MDC06 1-dagsgruppe, pat. Mindst 7 år)	Sundhedsdatastyrelsen (2024)[93]

	Diagnose kode/DRG code	Unit cost (DKK)/DRG tariff	Source
Pneumonia	A (DJ189)Pneu-moni UNS/04MA13	43,907.00 (Lungebetændelse og pleuritis, pat. Mindst 60 år, lang)	Sundhedsdatastyrelsen (2024)[93]

11.6 Subsequent treatment costs

Subsequent treatment costs were estimated by dividing the total costs of subsequent treatment by the total duration of the treatment in days (e.g., for chemotherapy costs per administration × 20.16 weeks ÷ 2, as administration frequency is Q2W). This daily cost of treatment was then divided by the mean time in the PD 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 PD (1,271.07 days) was estimated based on the restricted mean survival time (t = 40) in the PD state for the NIVO+IPI arm using the CM 142 data. The time in the PD state for PEMBRO was assumed equal to NIVO+IPI.

Table 58 summarises the medicines of subsequent treatments; Table 59 presents costs per administration and the duration per course of subsequent treatments. Vial sharing was assumed for cetuximab and bevacizumab. The average administration costs were based on the costs per administration divided by the mean doses received. In Table 60, the percentage of patients receiving each subsequent treatment is documented. For the patients receiving first-line IO treatments, based on previous assessment of PEMBRO by the DMC, it was assumed that 80% of patients received chemotherapy as subsequent treatment and 75% of these received FOLFIRI and 25% received FOLFIRI + cetuximab.[37]

Table 58. Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
FOLFIRI				
Irinotecan	180 mg/m^2	100%	Q2W	No
Fluorouracil bolus	400 mg/m^2	100%	Q2W	No
Fluorouracil infusion	2,400 mg/m^2	100%	Q2W	No
Calcium folinate	400 mg/m^2	100%	Q2W	No
FOLFIRI + cetuximab				
Irinotecan	180 mg/m^2	100%	Q2W	No

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Fluorouracil bolus	400 mg/m^2	100%	Q2W	No
Fluorouracil infusion	2,400 mg/m^2	100%	Q2W	No
Calcium folinate	400 mg/m^2	100%	Q2W	No
Cetuximab	500 mg/m^2	100%	Q2W	Yes

Table 59. Medicines of subsequent treatments: costs per administration and the duration per course of subsequent treatments

Medicine	Cost per administration (DKK)	Administration frequency	Administration route	Mean time on subsequent treatment (weeks)	Reference
FOLFIRI	4,190.00	Q2W	Complex IV	20.16	Medicinrådet (2021)[7]
FOLFIRI + cetuximab	16,594.11	Q2W	Complex IV	20.16	Medicinrådet (2021)[7]

Table 60. Distribution of subsequent therapy according to the first-line intervention or comparator administered

Medicine	FOLFIRI	FOLFIRI + cetuximab	Mono IO therapy	Combo IO therapy	Reference
NIVO+IPI	75%	25%	0%	0%	Assumed equal to PEMBRO
PEMBRO	75%	25%	0%	0%	Medicinrådet (2021)[7]

11.7 Patient costs

The costs incurred by patients as a consequence of the medicine treatment (transport costs and time spent) were included in the model and are presented in Table 61. It is assumed that administration and disease monitoring occur during the same hospital visit.

Table 61. Patient costs used in the model

Activity	Time spent [minutes, hours, days]	Reference
Travel costs	Average distance to healthcare professional: 20 km	Medicinraadet (2024)[95]
	Travel cost per km: DKK 3.73	
Patient cost	Hourly wage: DKK 203.0	Medicinraadet (2024)[95]

Activity	Time spent [minutes, hours, days]	Reference
	Hours per visit : 4	Medicinrådet (2021)[7]
	Average number of visits per health state per cycle	
	Progressed-free health state: 2 (on treatment) or 1 (off treatment)	Equal to the frequency of disease monitoring visit (Medicinrådet (2021)[7])
	Progressed disease health state: 0.17	Equal to the frequency of disease monitoring visit (Medicinrådet (2021)[7])

11.8 Other costs (e.g., costs for home care nurses, outpatient rehabilitation, and palliative care cost)

Not applicable.

12 Results

12.1 Base case overview

A summary of the base-case model inputs can be found in Table 62.

Table 62. Base-case overview

Feature	Description
Comparator	PEMBRO
Type of model	Semi-Markov model
Time horizon	40 years (lifetime)
Treatment line	First line. Subsequent treatment lines not included.
Measurement and valuation of health effects	HRQoL measured with EQ-5D-3L in CM 8HW. Danish population weights were used to estimate health-state utility values.
Costs included	▪ Drug-related costs — Drug acquisition costs — Drug administration costs — AE costs ▪ Resource use costs ▪ Subsequent treatment costs ▪ Patient time and travel costs

Feature	Description
Dosage of medicine	Based on patient weight
Average time on treatment	▪ NIVO+IPI induction: 3.61 doses ▪ NIVO maintenance: 11.9 doses ▪ PEMBRO: 16.09 doses
Transition probability model	
NIVO+IPI: PF to PD	Generalised gamma based on CM 8HW data
All treatments: PF to Death	Age-specific background mortality
All treatments: PD to Death	Log-logistic based on CM 142 data
PEMBRO: PF to PD	Generalised gamma based on unanchored MAIC between CM 8HW and KN-177 data
Average time in model health state	
PF	▪ NIVO+IPI: 12.79 years ▪ PEMBRO: 7.80 years
PD	▪ NIVO+IPI: 2.19 years ▪ PEMBRO: 3.21 years

12.1.1 Base case results

Table 63 presents the base-case results for the comparison of NIVO+IPI against PEMBRO.

Table 63. Base-case results, discounted estimates

	NIVO+IPI	PEMBRO	Difference
Medicine costs	DKK 617,659.68	DKK 486,699.96	DKK 130,959.71
Medicine costs – co-administration	NA	NA	NA
Administration	DKK 24,314.42	DKK 12,488.00	DKK 11,826.42
Disease management costs	DKK 292,691.69	DKK 137,934.48	DKK 154,757.21
Costs associated with management of AEs	DKK 1,303.25	DKK 1,793.01	DKK (489.76)
Subsequent treatment costs	DKK 31,802.96	DKK 48,194.31	DKK (16,391.36)
Patient costs	DKK 128,890.76	DKK 85,709.47	DKK 43,181.29

	NIVO+IPI	PEMBRO	Difference
Palliative care costs	DKK 0.00	DKK 0.00	DKK 0.00
Total costs	**DKK 1,194,552.27**	**DKK 833,475.52**	**DKK 361,076.74**
Life-years gained (PF)	[redacted]	[redacted]	[redacted]
Life-years gained (PD)	[redacted]	[redacted]	[redacted]
Total life-years	[redacted]	[redacted]	[redacted]
QALYs (PF)	[redacted]	[redacted]	[redacted]
QALYs (PD)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life-year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Table 65 presents the upper and lower bound values for each parameter tested in the one-way sensitivity analysis and the ICERs.

Table 64. One-way sensitivity analyses results for NIVO+IPI versus PEMBRO

	Value	Change (lower; upper bound)	Incremental cost (DKK) (lower; upper bound)	Incremental benefit (QALYs) (lower; upper bound)	ICER (DKK/QALY) (lower; upper bound)
Base case					[redacted]
NIVO+IPI maintenance: mean doses	11.9	(7.24; 16.56)	(127,285.10; 514,644.08)	[redacted]	[redacted]
PEMBRO: mean doses	16.09	(9.78; 22.39)	(538,546.84; 155,476.74)	[redacted]	[redacted]

	Value	Change (lower; upper bound)	Incremental cost (DKK) (lower; upper bound)	Incremental benefit (QALYs) (lower; upper bound)	ICER (DKK/QALY) (lower; upper bound)
NIVO+IPI induction: mean doses	3.61	(2.19; 5.03)	(248,054.25; 399,616.99)	[redacted]	[redacted]
Consultation outpatient appointment: units used - PF off treatment	1.00	(0.38; 1.92)	(264,394.92; 411,831.55)	[redacted]	[redacted]
Consultation outpatient appointment costs	1,561	(1,010.20; 2,229.74)	(283,459.55; 372,874.30)	[redacted]	[redacted]
CT scan: units used – PF off treatment	0.30	(0.19; 0.43)	(310,779.59; 339,704.62)	[redacted]	[redacted]
CT scan costs	2,021	(1,307.88; 2,886.80)	(309,468.89; 341,295.96)	[redacted]	[redacted]
Progressed disease utility estimate	0.788	(0.756; 0.818)	(323,843.51; 323,843.51)	[redacted]	[redacted]
Progression free utility estimate	0.816	(0.795; 0.836)	(323,843.51; 323,843.51)	[redacted]	[redacted]
Average weight	70.5	(68.5; 72.5)	(320,057.74; 327,629.28)	[redacted]	[redacted]

CT = computed tomography; ICER = incremental cost-effectiveness ratio; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab; PF = progression free; QALY = quality-adjusted life-year.

12.2.2 Probabilistic sensitivity analyses

Probabilistic results can be found in Table 65 and were consistent with the deterministic results, suggesting model stability. Figure 36 presents the cost-effectiveness plane comparison of incremental costs and QALYs for NIVO+IPI versus PEMBRO. Figure 37 shows the cost-effectiveness acceptability curves of NIVO+IPI and PEMBRO. Below a threshold of DKK 165,000 PEMBRO had the highest probability of being cost-effective, hereafter NIVO+IPI had the highest probability of being cost-effective.

Table 65. Probabilistic results

Comparator	Incremental costs	Incremental QALYs	ICER	Deterministic ICER
PEMBRO	DKK 323,724.11	[redacted]	[redacted]	[redacted]

Figure 36. Cost-effectiveness plane comparison of incremental costs and QALYs for NIVO+IPI versus PEMBRO

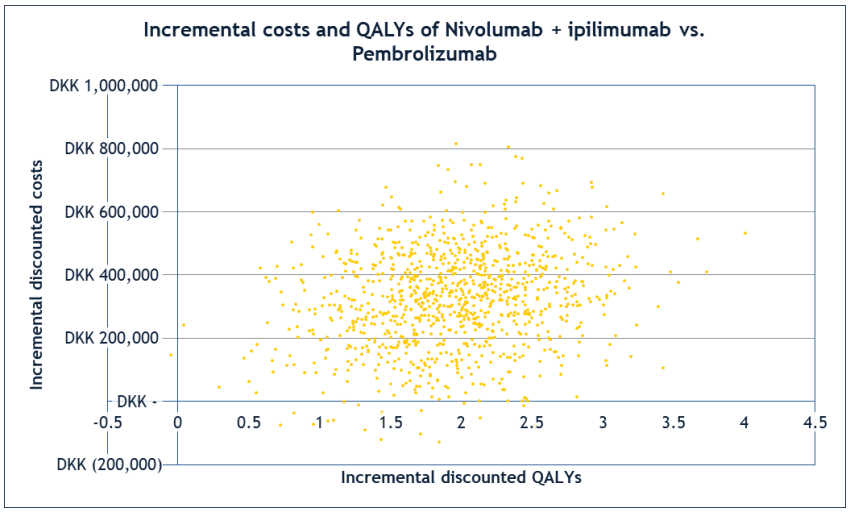


Figure 37. Cost-effectiveness acceptability curves

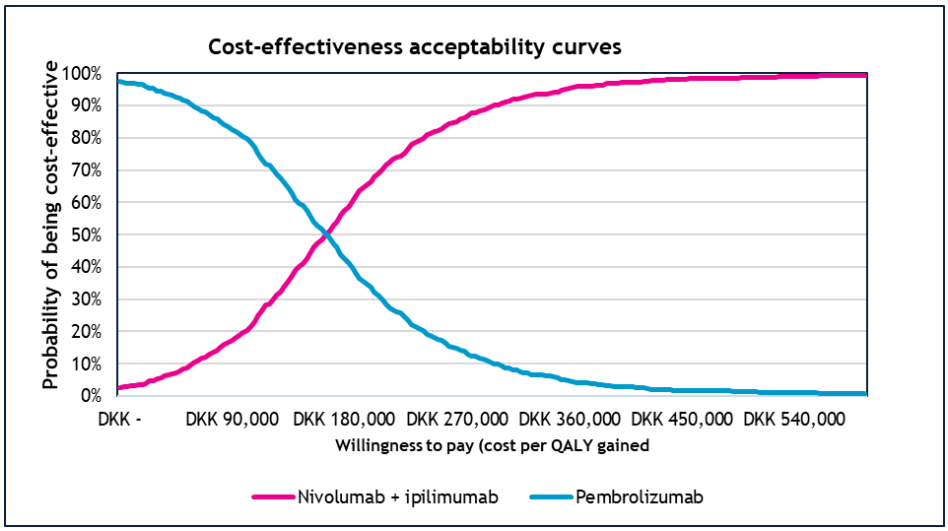


Table 67Table 66 presents the results of the scenario analysis that was conducted. Notably, when the second-best fit curve for extrapolating PFS is used, the ICER decreases slightly. Adjusted or unadjusted anchored MAIC instead of unanchored MAIC (base-case) results in a significant increase in incremental QALYs gained, showing that the base-case analysis is conservative regarding treatment effect. Conversely, the use of a constant treatment effect reduced the incremental QALYs gained some. Using CM 142 instead of

general population mortality for estimating the PF-to-Death transition causes a slight increase in the ICER. Overall, the scenario analyses confirm the robustness of NIVO+IPI as a cost-effective option.

Table 66. Summary of results of the scenario analysis

Scenarios	Incremental costs (DKK)	Incremental QALYs	ICER (DKK)
Base case	323,843.51	[redacted]	[redacted]
Unadjusted anchored MAIC	373,307.50	[redacted]	[redacted]
Adjusted anchored MAIC	370,224.45	[redacted]	[redacted]
Constant hazard	298,233.82	[redacted]	[redacted]
CM 142 instead of general population mortality	308,904.49	[redacted]	[redacted]
Extrapolation for PFS using second-best fit (log-normal for NIVO+IPI)	306,789.65	[redacted]	[redacted]
Q3W PEMBRO	251,684.96	[redacted]	[redacted]
Fixed dose of 480mg for NIVO monotherapy for patients with body weight of 80 kg or more	298,752.16	[redacted]	[redacted]

13 Budget impact analysis

Number of patients (including assumptions of market share)

The uptake of NIVO+IPI and PEMBRO is based on assumptions; NIVO+IPI is assumed to get its share from PEMBRO. Table 67 presents the number of new patients expected to be treated over the next 5-year period if NIVO+IPI is introduced.

Table 67. **Number of new patients expected to be treated over the next 5-year period if NIVO+IPI is introduced (adjusted for market share)**

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-recommendation					
NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEMBRO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 68 presents the expected budget impact of recommending NIVO+IPI for the indication over the 5-year time horizon.

Table 68. **Expected budget impact of recommending the medicine for the indication**

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact of the recommendation (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14 List of experts

Not applicable.

15 References

1. OPDIVO SmPC. Bristol Myers Squibb. OPDIVO 10 mg/mL concentrate for solution for infusion. 22 July 2024. https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf. Accessed 22 August 2024.
2. YERVOY SmPC. Bristol Myers Squibb. YERVOY 5 mg/ml concentrate for solution for infusion. 22 July 2024. https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf. Accessed 22 August 2024.
3. DCCG. Danish Colorectal Cancer Group. Kliniske retningslinjer. Medicinsk onkologisk behandling af metastaserende kolorektal cancer. 2 October 2023. https://www.dmcg.dk/siteassets/kliniske-retningslinjer---skabeloner-og-vejledninger/kliniske-retningslinjer-opdelt-pa-dmcg/dccg/dccg_med_onk_beh_meta_kol_v1.0_admgodk181023.pdf. Accessed 9 July 2024.
4. DCCG. Danish Colorectal Cancer Group. Landsdækkende database for kræft i tyk- og endetarm. National årsrapport 2022 1. Januar 2022 – 31. December 2022. 2 October 2023. https://dccg.dk/wp-content/uploads/2023/10/4681_dccg-aarsrapport-2022_offentliggjort-version.pdf. Accessed 9 July 2024.
5. Houlind Petersen N. Onkologyst Tidsskrift. Algoritme kan finde kræft-tilbagefald i registre. 4 April 2023. https://onkologisktidsskrift.dk/behandlinger/tarmkraeft/2855-algoritme-kan-finde-kraeft-tilbagefald-i-registre.html. Accessed 9 July 2024.
6. Nors J, Mattesen TB, Cronin-Fenton D, Mailhac A, Bramsen JB, Gotschalck KA, et al. Identifying recurrences among non-metastatic colorectal cancer patients using National Health Data Registries: validation and optimization of a registry-based algorithm in a Modern Danish Cohort. Clin Epidemiol. 2023;15:241-50.
7. Medicinrådet. Medicinrådets anbefaling vedrørende pembrolizumab til behandling af MMR-deficient (MSI-H/dMMR) metastatisk kolorektalkræft. 21 September 2021. https://medicinraadet-classic.azureedge.net/media/mw3l1qf0/medicinr%C3%A5dets-anbefaling-vedr-pembrolizumab-til-mcrc-vers-1-0_adlegacy.pdf. Accessed 9 July 2024.

8. Wensink GE, Elferink MAG, May AM, Mol L, Hamers PAH, Bakker SD, et al. Survival of patients with deficient mismatch repair metastatic colorectal cancer in the pre-immunotherapy era. Br J Cancer. 2021 Jan;124(2):399-406.
9. Shiu K, André T, Kim TW, Vittrup Jensen B, Jensen LH, Punt CJA, et al. Pembrolizumab versus chemotherapy in microsatellite instability–high/mismatch repair–deficient metastatic colorectal cancer: 5-year follow-up of the randomized phase III KEYNOTE-177 study. Ann Oncol. 2023;34:S1271-72.
10. BMS data on file. Bristol Myers Squibb. Interim clinical study report for study CA2098HW. 2024.
11. IARC. International Agency for Research on Cancer. Absolute numbers, mortality, both sexes, in 2022. 2022. https://gco.iarc.who.int/today/en/dataviz/bars?types=1&mode=cancer&sort_by=value0&key=total&group_populations=1. Accessed 22 August 2024.
12. Lee JJ, Sun W. Options for second-line treatment in metastatic colorectal cancer. Clin Adv Hematol Oncol. 2016 Jan;14(1):46-54.
13. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, Group EGW. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 Suppl 3:iii1-9.
14. National Cancer Institute. Cancer stat facts: colorectal cancer. 2020. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed 2 December 2024.
15. Copija A, Waniczek D, Witkos A, Walkiewicz K, Nowakowska-Zajdel E. Clinical significance and prognostic relevance of microsatellite instability in sporadic colorectal cancer patients. Int J Mol Sci. 2017 Jan 6;18(1):107.
16. ACS. American Cancer Society. Colorectal cancer facts & figures 2020-2022. 2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf. Accessed 22 August 2024.
17. Fletcher RH. The diagnosis of colorectal cancer in patients with symptoms: finding a needle in a haystack. BMC Med. 2009 Apr 17;7(1):18.
18. Power E, Simon A, Juszczyk D, Hiom S, Wardle J. Assessing awareness of colorectal cancer symptoms: measure development and results from a population survey in the UK. BMC Cancer. 2011 Aug 23;11(1):366.
19. Johnson CM, Wei C, Ensor JE, Smolenski DJ, Amos CI, Levin B, et al. Meta-analyses of colorectal cancer risk factors. Cancer Causes Control. 2013 Jun;24(6):1207-22.
20. De' Angelis GL, Bottarelli L, Azzoni C, De' Angelis N, Leandro G, Di Mario F, et al. Microsatellite instability in colorectal cancer. Acta Biomed. 2018 Dec 17;89(9-S):97-101.
21. Neves ALF, Barbosa LER, Teixeira JPMdA. Prognosis in colorectal cancer beyond TNM. J Coloproctol. 2021;40(04):404-11.
22. Gelsomino F, Barbolini M, Spallanzani A, Pugliese G, Cascinu S. The evolving role of microsatellite instability in colorectal cancer: a review. Cancer Treat Rev. 2016 Dec;51:19-26.
23. Duval A, Hamelin R. Genetic instability in human mismatch repair deficient cancers. Ann Genet. 2002 Apr-Jun;45(2):71-5.
24. Gutierrez C, Ogino S, Meyerhardt JA, Iorgulescu JB. The prevalence and prognosis of microsatellite instability-high/mismatch repair-deficient colorectal adenocarcinomas in the United States. JCO Precis Oncol. 2023 Jan;7(7):e2200179.
25. Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D, et al. Mismatch repair status and BRAF mutation status in metastatic colorectal

cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res. 2014 Oct 15;20(20):5322-30.
26. ASCO. American Society of Clinical Oncology. Colorectal cancer: stages. 2022. https://www.cancer.net/cancer-types/colorectal-cancer/stages. Accessed 13 October 2022.
27. Kim CG, Ahn JB, Jung M, Beom SH, Kim C, Kim JH, et al. Effects of microsatellite instability on recurrence patterns and outcomes in colorectal cancers. Br J Cancer. 2016 Jun 28;115(1):25-33.
28. Zainal Abidin MN, Omar MS, Islahudin F, Mohamed Shah N. The survival impact of palliative chemotherapy dose modifications on metastatic colon cancer. BMC Cancer. 2022 Jul 4;22(1):731.
29. Andre T, Shiu K-K, Kim TW, Jensen BV, Jensen LH, Punt CJA, et al. Final overall survival for the phase III KN177 study: pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). J Clin Oncol. 2021;39(15_suppl):3500.
30. NORDCAN. Association of the Nordic Cancer Registries. Colorectal cancer in Denmark 2021. 2 October 2023. https://nordcan.iarc.fr/en/dataviz/prevalence_table?years=2021&years_available=1943_2021&sexes=0&cancers=520. Accessed 9 July 2024.
31. DCCG. Danish Colorectal Cancer Group. DCCG's nationale retningslinier for diagnostik og behandling af kolorektal cancer. Version 4. 2018. https://dccg.dk/wp-content/uploads/2023/07/2018_Adj_Rektum_v4.0.pdf. Accessed 9 July 2024.
32. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010 Jul 1;28(19):3167-75.
33. Menzies AM, Long GV. New combinations and immunotherapies for melanoma: latest evidence and clinical utility. Ther Adv Med Oncol. 2013 Sep;5(5):278-85.
34. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov. 2018 Sep;8(9):1069-86.
35. OPDIVO PI. Bristol Myers Squibb. OPDIVO (nivolumab) injection, for intravenous use. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125554Orig1s121lbl.pdf. Accessed 26 February 2024.
36. Keytruda SmPC. Merck Sharp & Dohme B.V. KEYTRUDA 25 mg/mL concentrate for solution for infusion. 16 September 2024. https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf. Accessed 23 October 2024.
37. DMC. Danish Medicines Council. Appendix to the Medical Council's recommendation regarding pembrolizumab for the treatment of MMR-(MSI-H/dMMR) metastatic colorectal cancer. 2021. https://medicinraadet-classic.azureedge.net/media/j2blfrey/bilag-til-medicinr%C3%A5dets-anbefaling-vedr-pembrolizumab-til-mcrc-vers-1-0_adlegacy.pdf. Accessed 23 August 2024.
38. BMS data on file. Bristol Myers Squibb. Clinical protocol CA2098HW. 2023.
39. Andre T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020 Dec 3;383(23):2207-18.
40. Roodhart JML. Evaluating the patient-level association between progression-free survival and overall survival in microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer (MSI-H/dMMR mCRC) treated with immune checkpoint inhibitors. Ann Oncol. 2024;35:S27.

41. Andre T, Elez E, Van Cutsem E, Jensen LH, Bennouna J, Mendez G, et al. Nivolumab plus ipilimumab in microsatellite-instability-high metastatic colorectal cancer. N Engl J Med. 2024 Nov 28;391(21):2014-26.
42. Andre T, Elez E, Van Cutsem E, Jensen LH, Bennouna J, Mendez G, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): first results of the CheckMate 8HW study. J Clin Oncol. 2024;42(3_suppl):LBA768-LBA.
43. Lenz H-J, Lonardi S, Elez E, Van Cutsem E, Jensen LH, Bennouna J, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): expanded efficacy analysis from CheckMate 8HW. J Clin Oncol. 2024;42(16_suppl):3503.
44. Shiu K, André T, Kim TW, Vittrup Jensen B, Jensen LH, Punt CJA. Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomized phase III KEYNOTE-177 study. Presented at European Society for Medical Oncology (ESMO); 20-24 October 2023.
45. Diaz LA, Jr., Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2022 May;23(5):659-70.
46. Lenz H-J, Overman MJ, Van Cutsem E, Limon ML, Wong KYM, Hendlisz A, et al. First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 64-month (mo) follow-up from CheckMate 142. J Clin Oncol. 2024;42(3_suppl):97.
47. Overman MJ, Lenz H-J, Andre T, Aglietta M, Wong MK, Luppi G, et al. Nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): five-year follow-up from CheckMate 142. J Clin Oncol. 2022;40(16_suppl):3510.
48. Andre T, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Ann Oncol. 2022 Oct;33(10):1052-60.
49. Lenz HJ, Van Cutsem E, Luisa Limon M, Wong KYM, Hendlisz A, Aglietta M, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 study. J Clin Oncol. 2022 Jan 10;40(2):161-70.
50. Freeman K, Connock M, Cummins E, Gurung T, Taylor-Phillips S, Court R. Coventry: Warwick Evidence. Fluorouracil plasma monitoring: the My5-FU assay for guiding dose adjustment in patients receiving fluorouracil chemotherapy by continuous infusion. 2014.
51. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008 Dec;62(3):374-80.
52. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ. 2013 Oct;14(5):749-59.

53. Mai K, Fassnacht M, Führer-Sakel D, Honegger JB, Weber MM, Kroiss M. The diagnosis and management of endocrine side effects of immune checkpoint inhibitors. Dtsch Arztebl Int. 2021 Jun 11;118(Forthcoming):389-96.
54. BMS data on file. Bristol Myers Squibb. Interim analysis of second co-primary endpoint of CheckMate 8HW. 2024.
55. BMS data on file. Bristol Myers Squibb. A phase 3 randomized clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. 2024.
56. BMS data on file. Bristol Myers Squibb. Interim clinical study report for study CA2098HW-section 14 tables. 2024.
57. BMS data on file. Bristol Myers Squibb. Interim clinical study report for study CA2098HW-section 14 figures. 2024.
58. BMS data on file. Bristol Myers Squibb. PFS forest plot from CheckMate 8HW locally confirmed population. 2024.
59. Andre T, Lonardi S, Lenz HJ, Jensen LH, Van Cutsem E, Touchefeu Y, et al. 541P - Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): subgroup efficacy and expanded safety analyses from CheckMate 8HW [poster]. Presented at ESMO Congress 2024; 13-17 September 2024. Barcelona, Spain. https://oncologypro.esmo.org/meeting-resources/esmo-congress-2024/nivolumab-nivo-plus-ipilimumab-ipi-vs-chemotherapy-chemo-as-first-line-1l-treatment-for-microsatellite-instability-high-mismatch-repair-def. Accessed 14 October 2024.
60. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
61. Franko J, Shi Q, Meyers JP, Maughan TS, Adams RA, Seymour MT, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol. 2016 Dec;17(12):1709-19.
62. Goey KKH, Sørbye H, Glimelius B, Adams RA, André T, Arnold D, et al. Consensus statement on essential patient characteristics in systemic treatment trials for metastatic colorectal cancer: supported by the ARCAD Group. Eur J Cancer. 2018 Sep;100:35-45.
63. NICE. National Institute for Health and Care Excellence. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [TA709]. 23 June 2021. https://www.nice.org.uk/guidance/ta709. Accessed 11 April 2024.
64. Medicinraadet. Bilag til Medicinrådets anbefaling vedrørende nivolumab som adjuverende behandling til patienter med kræft i spiserør eller mavemund efter neoadjuvant kemoradioterapi og radikal resektion uden komplet patologisk remission. 2022. https://medicinraadet-classic.azureedge.net/media/xdkf43e0/bilag_til_medicinr%C3%A5dets_anbefaling_vedr-_nivolumab_som_adjuv-_behand-_til_kr%C3%A6ft_i_spiser%C3%B8r_el-_mavemund-vers-_1-0_adlegacy.pdf. Accessed 11 December 2024.
65. Canada's Drug Agency. Canadian Journal of Health Technologies. Reimbursement review: pembrolizumab (Keytruda). September 2021. https://www.cadth.ca/sites/default/files/DRR/2021/PC0235-Keytruda-Combined.pdf. Accessed 21 March 2023.

66. Latimer N. Decision Support Unit, ScHARR, University of Sheffield. NICE DSU Technical Support Document 14. Survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. 2013. https://www.sheffield.ac.uk/nice-dsu/tsds/survival-analysis. Accessed 27 November 2024.
67. Rutherford M, Lambert P, Sweeting M, Pennington B, Crowther M, Abrams KR. NICE DSU Technical Support Document 21. Flexible methods for survival analysis. 2020. http://nicedsu.org.uk/. Accessed 14 December 2020.
68. Palmer S, Borget I, Friede T, Husereau D, Karnon J, Kearns B, et al. A Guide to selecting flexible survival models to inform economic evaluations of cancer immunotherapies. Value Health. 2023 Feb;26(2):185-92.
69. Statistics Denmark. HISB8: life table (2 years tables) by sex, age and life table. 2024. https://www.statbank.dk/HISB8. Accessed 23 October 2024.
70. BMS data on file. Bristol Myers Squibb. Cost-effectiveness analysis of nivolumab + ipilimumab for 1L MSI-H/dMMR mCRC. 2024.
71. BMS data on file. Bristol Myers Squibb. CA2098HW: Health-related quality of life analysis. Results for health-related quality of life analysis in patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer treated with nivolumab alone, nivolumab in combination with ipilimumab, or chemotherapy (CheckMate 8HW). November 2023 database lock. 5 June 2024.
72. Andre T, Amonkar M, Norquist JM, Shiu KK, Kim TW, Jensen BV, et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021 May;22(5):665-77.
73. Giesinger JM, Efficace F, Aaronson N, Calvert M, Kyte D, Cottone F, et al. Past and current practice of patient-reported outcome measurement in randomized cancer clinical trials: a systematic review. Value Health. 2021 Apr;24(4):585-91.
74. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44.
75. BMS data on file. Bristol Myers Squibb. Analyses of health-related quality of life in patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer treated with nivolumab alone, nivolumab in combination with ipilimumab, or chemotherapy (CheckMate 8HW), utilities by health state analysis report (database lock: 15 November 2023). 2024.
76. Cnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Stat Med. 1997 Oct 30;16(20):2349-80.
77. Gałecki A, Burzykowski T. Springer. Linear mixed-effects models using R. 2013. https://link.springer.com/book/10.1007/978-1-4614-3900-4. Accessed 24 October 2024.
78. Medicinrådet. The Danish Medicines Council methods guide for assessing new pharmaceuticals. 2021. https://medicinraadet.dk/media/5eibukbr/the-danish-medicines-council-methods-guide-for-assessing-new-pharmaceuticals-version-1-3.pdf. Accessed 11 December 2024.
79. van Hout BA, Shaw JW. Mapping EQ-5D-3L to EQ-5D-5L. Value Health. 2021 Sep;24(9):1285-93.
80. Jensen CE, Sorensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L value set: a hybrid model using cTTO and DCE data. Appl Health Econ Health Policy. 2021 Jul;19(4):579-91.

81. NICE. National Institute for Health and Care Excellence. Single Technology Appraisal. Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]. Committee papers. October 2020. https://www.nice.org.uk/guidance/ta716/evidence/committee-papers-pdf-9194497885. Accessed 25 October 2024.
82. BMS data on file. Bristol Myers Squibb. A phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma. (clinical study report). 21 September 2017.
83. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin. 2010 May;26(5):1091-6.
84. Shabaruddin FH, Chen LC, Elliott RA, Payne K. A systematic review of utility values for chemotherapy-related adverse events. Pharmacoeconomics. 2013 Apr;31(4):277-88.
85. VEG105192 clinical study report. 16 April 2010. https://www.nice.org.uk/guidance/TA215/documents/renal-cell-carcinoma-first-line-metastatic-pazopanib-manufacturer-submission-submission2. Accessed 12 November 2024.
86. Laegemiddlestyrelsen (Danish Medicines Agency). Laegemiddlestyrelsen (Danish Medicines Agency),. 2024. https://www.medicinpriser.dk. Accessed 23 October 2024.
87. Laegemiddlestyrelsen (Danish Medicines Agency). Opdivo 539385 - 40mg/4ml. 2024. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=539385. Accessed 23 October 2024.
88. Laegemiddlestyrelsen (Danish Medicines Agency). Opdivo 579240 - 100mg/10ml. 2024. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=579240. Accessed 23 October 2024.
89. Laegemiddlestyrelsen (Danish Medicines Agency). Opdivo 479954 240mg/24ml. 2024. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=479954. Accessed 23 October 2024.
90. Laegemiddlestyrelsen (Danish Medicines Agency). Yervoy 597433 5mg/ml. 2024. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=597433. Accessed 23 October 2024.
91. Laegemiddlestyrelsen (Danish Medicines Agency). Yervoy 199940 5mg/ml. 2024. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=199940. Accessed 23 October 2024.
92. Laegemiddlestyrelsen (Danish Medicines Agency). Keyrtuda 585359 25mg/ml. 2024. https://www.medicinpriser.dk/Default.aspx?id=15&vnr=585359. Accessed 23 October 2024.
93. Sundhedsdatastyrelsen. DRG tariffs 2024. 2024. https://sundhedsdatastyrelsen.dk/data-og-registre/sundhedsoekonomi/drg-takster/takster-2024. Accessed 23 December 2024.
94. Rigshospitalets Labportal. Test code for liver function tests included (codes): ALAT - NPU19651, ASAT - NPU19654, ALB - NPU19673, BASPH – NPU53077, GGT – NPU19657. 2024. https://labportal.rh.dk/Labportal.asp. Accessed 23 October 2024.
95. Medicinraadet. Værdisætning af enhedsomkostninger. 2024. https://medicinraadet.dk/media/gpjgcotu/v%C3%A6rdis%C3%A6tning-af-enhedsomkostninger-vers-1-7.pdf Accessed 23 October 2024.

Application for the assessment of nivolumab + ipilimumab for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC): Appendices

Table of contents

Tables and Figures

Appendix A. Main characteristics of studies included

Three studies that provide clinical evidence in this submission are described. CheckMate 8HW (CM 8HW) is the main clinical trial in support of nivolumab + ipilimumab (NIVO+IPI) in CRC (Table 1), CM 142 (Table 2) provides additional supporting information used in the economic model, KEYNOTE-177 (KN-177) is the main clinical trial in support of the comparator, pembrolizumab (PEMBRO) (Table 3).

Table 1. Main characteristics of CM 8HW

CM 8HW	NCT04008030
Objective	To compare the clinical benefit, as measured by PFS, ORR, and OS, achieved by NIVO+IPI, NIVO monotherapy or chemotherapy in participants with MSI-H or dMMR mCRC. Specifically: ▪ To compare the clinical benefit of NIVO+IPI versus chemotherapy as first-line treatment for patients with dMMR/MSI-H mCRC ▪ To compare the clinical benefit of NIVO+IPI with NIVO monotherapy in all lines of treatment in patients with dMMR/MSI-H mCRC Only the first objective is relevant to the current review and is the focus of this submission.
Publications – title, author, journal, year	▪ BMS Data on file Unpublished data 2024.: Nivolumab Clinical Study Report. ▪ Andre T, Elez E, Van Cutsem E, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): first results of the CheckMate 8HW study. J Clin Oncol. 2024;42(suppl 3). DOI:10.1200/JCO.2024.42.3_suppl.LBA768 ▪ Lenz HZ, Lonardi S, Elez E, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Expanded efficacy analysis from CheckMate 8HW. J Clin Oncol.3503-3503(2024). DOI:10.1200/JCO.2024.42.16_suppl.3503 ▪ Andre T, Elez E, Van Cutsem E, Jensen LH, Bennouna J, Mendez G, et al. Nivolumab plus ipilimumab in microsatellite-instability-high metastatic colorectal cancer. N Engl J Med. 2024 Nov 28;391(21):2014-2026. doi: 10.1056/NEJMoa2402141.
Study type and design	A phase 3 trial evaluating first-line NIVO+IPI in patients with MSI-H/dMMR mCRC. The study consists of 3 arms: NIVO alone (Arm A), NIVO in combination with IPI (Arm B), or investigator's choice chemotherapy (Arm C) in participants with MSI-H/dMMR mCRC.[1] Study enrolment consisted of 2 sequential parts: enrolment in part 1 was open to all patients regardless of line of therapy, while enrolment in part 2 was only open to patients who had not received prior therapy for

CM 8HW	NCT04008030
	metastatic disease (i.e., patients receiving 1L therapy). Enrolment in part 2 started immediately after part 1 enrolment.[1] In part 1, patients receiving treatment in the 1L and 2L were randomised between the three arms in a 2:2:1 ratio, while patients receiving treatment in ≥ 3L were randomised to Arm A (NIVO monotherapy) or Arm B (NIVO+ IPI) in a 1:1 ratio.[1] Only the first-line setting, and treatment with NIVO+IPI vs. chemo are relevant to the current indication.
Sample size (n)	Approximately 831 patients with locally confirmed MSI-H/dMMR mCRC were randomised across lines of therapy during part 1 and part 2 enrolment. An additional 10 patients from the China were randomised into the NIVO+IPI and chemotherapy arms.[1] In the 1L setting, 202 patients were randomised to NIVO+IPI and 101 to chemo. [1]
Main inclusion criteria	▪ Histologically confirmed recurrent or mCRC irrespective of prior treatment history with chemotherapy and/or targeted agents not amenable to surgery (applicable only during Part 1 enrolment of the study) ▪ Histologically confirmed recurrent or mCRC with no prior treatment history with chemotherapy and/or targeted agents for metastatic disease and not amenable to surgery (applicable during Part 2 enrolment of the study) ▪ Known MSI-H or dMMR status per local standard of practice ▪ ECOG performance status ≤ 1
Main exclusion criteria	▪ An active, known or suspected autoimmune disease ▪ History of interstitial lung disease or pneumonitis ▪ Known history of positive test for HIV or known AIDS
Intervention	Patients receiving treatment in the 1L and 2L were randomly assigned in a 2:2:1 ratio to receive interventions as below: ▪ NIVO monotherapy (Arm A): NIVO 240 mg every 2 weeks for 6 doses, followed thereafter by NIVO 480 mg every 4 weeks ▪ NIVO+IPI combination (Arm B): NIVO 240 mg plus IPI 1 mg/kg every 3 weeks for 4 doses, followed thereafter by NIVO 480 mg every 4 weeks. All patients received treatment of NIVO until disease progression or unacceptable toxicity—up to a maximum of 2 years. Number of patients: in the 1L setting, 202 of 303 patients were randomised to receive NIVO+IPI
Comparator(s)	Investigator's choice chemotherapy (Arm C): the investigator's choice of FOLFOX or FOLFIRI, which could be combined with bevacizumab or cetuximab. Number patients: in the 1L setting, 101 of 303 patients were randomised to receive chemotherapy.

CM 8HW	NCT04008030
	Patients assigned to chemotherapy could cross over to receive NIVO+IPI at the time of disease progression.
Follow-up time	Median follow-up: [redacted] with a minimum follow-up of [redacted] (interim analysis based on a clinical data cutoff on 12 October 2023 and database lock on 15 November 2023) for analysis of NIVO+IPI vs. chemotherapy.[1]
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	For this interim analysis the primary endpoint was a comparison of: ▪ PFS per BICR in 1L patients with centrally confirmed MSI-H/dMMR mCRC receiving NIVO+IPI or chemo. Secondary endpoints were comparisons of: ▪ PFS per BICR in 1L patients with locally confirmed MSI-H/dMMR mCRC receiving NIVO+IPI or chemo ▪ PFS per investigator in 1L patients with centrally confirmed MSI-H/dMMR mCRC receiving NIVO+IPI or chemo ▪ PFS per investigator in 1L patients with centrally confirmed by each central test (PCR and IHC) MSI-H/dMMR mCRC receiving NIVO+IPI or chemo Exploratory endpoints included association of biomarkers with efficacy and PFS2 in 1L patients with centrally confirmed MSI-H/dMMR; safety in all 1L treated patients and EORTC QLQ-C30), EQ-5D-3L and EQ-5D VAS in central and locally confirmed patients. Endpoints included in this application: ▪ PFS per BICR in 1L patients with locally confirmed MSI-H/dMMR mCRC receiving NIVO+IPI or chemo. The other primary endpoint (comparing PFS per BICR in all patients with centrally confirmed MSI-H/dMMR mCRC receiving either NIVO+IPI or NIVO alone) was not tested in this interim analysis, since it did not meet the required number of events to trigger its interim analysis
Method of analysis	To test for statistical significance, the primary endpoint was stratified via log-rank tests using tumour sidedness (left vs. right) as a stratification factor. HR between treatment arms was estimated via a stratified Cox proportional hazards model, with treatment arm as the only covariate and ties handled using the exact method.[2] PFS functions for each treatment arm were estimated using the KM product-limit method and displayed graphically. Log-log transformation methods were used to compute 2-sided 95% CI for mPFS in each treatment arm. Landmark analysis at 6 months and 12 months were presented along with the associated 95% CIs. Estimates were derived from the KM estimate and corresponding CIs derived based on the Greenwood formula for variance derivation and on log-log transformations applied on the survivor function. The source of PFS event (progression or death) and the status of

CM 8HW	NCT04008030
	patients who were censored in the PFS KM analysis was summarised by treatment arm [1].
Subgroup analyses	▪ Prespecified subgroup categories for PFS analysis were age, geographical region, site of the primary tumour, hepatic or pulmonary metastases versus other metastases, PD-L1 expression, and BRAF/KRAS/NRAS mutation status.
Other relevant information	The interim analysis based on 12 October 2023 data cut only includes [redacted] September 2024 database lock provides supporting information on the [redacted] Although the centrally confirmed MSI-H/dMMR population was the primary endpoint, the locally confirmed population equates to the ITT population and is more comparable with the population available for PEMBRO and is therefore the focus of this submission.

1L = first line; 2L = second line; AIDS = acquired immunodeficiency syndrome; BICR = Blinded Independent Central Review; dMMR = Mismatch Repair Deficient; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil + leucovorin + irinotecan; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; HIV = human immunodeficiency virus; IHC = immunohistochemistry; mCRC = metastatic colorectal cancer; MSI-H = Microsatellite Instability High; ORR = objective response rate; OS = overall survival; PCR = polymerase chain reaction; PFS = progression-free survival.

Sources: BMS data on file (2024)[1]; Andre et al. (2024)[3]; Lenz et al. (2024)[4]

Table 2. Main characteristics of CM 142

CM 142	NCT02060188
Objective	To compare the clinical benefit, as measured by PFS, ORR, and OS, achieved by NIVO+ IPI, NIVO monotherapy, or chemotherapy in participants with MSI-H or dMMR mCRC.
Publications – title, author, journal, year	▪ Lenz H, Overman MJ, Van Cutsem E, et al. First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 64-month (mo) follow-up from CheckMate 142. Journal of Clinical Oncology. 2024; 42(3_suppl), 97-97. https://doi.org/10.1200/JCO.2024.42.3_suppl.97 ▪ Overman MJ, Lenz HJ, Andre T, et al. Nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Five-year follow-up from CheckMate 142. Journal of Clinical Oncology. 2022. 40(16_suppl), 3510-3510. https://doi.org/10.1200/JCO.2022.40.16_suppl.3510 ▪ André T, Lonardi S, Wong KYM, et al. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Ann Oncol. 2022 Oct;33(10):1052-1060. doi: 10.1016/j.annonc.2022.06.008. Epub 2022 Jun 25. ▪ Lenz HJ, Van Cutsem E, Luisa Limon M, et al. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142

CM 142	NCT02060188
	Study. J Clin Oncol. 2022 Jan 10;40(2):161-170. doi: 10.1200/JCO.21.01015.
Study type and design	A multicohort, non-randomised phase 2 study evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC. The study design consisted of 3 separate cohorts: ▪ Cohort 1: NIVO monotherapy in 2L+ ▪ Cohort 2: NIVO and low-dose IPI in 2L+ ▪ Cohort 3: NIVO and low-dose IPI in 1L
Sample size (n)	▪ Cohort 1: NIVO monotherapy in 2L+ (n = 74) ▪ Cohort 2: NIVO and low-dose IPI in 2L+ (n = 119) ▪ Cohort 3: NIVO and low-dose IPI in 1L (n = 45)
Main inclusion criteria	▪ ECOG performance status of 0 to 1 ▪ Histologically confirmed recurrent or metastatic CRC ▪ Measurable disease per RECIST v1.1 ▪ Microsatellite instability expression detected by an accredited laboratory ▪ Participants enrolled into the C3 Cohort must have not had treatment for their metastatic disease
Main exclusion criteria	▪ Active brain metastases or leptomeningeal metastases ▪ 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 ▪ Prior malignancy active within the previous 3 years except for locally curable cancers ▪ Participants with active, known or suspected autoimmune disease ▪ Participants with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration
Intervention	▪ 2L+ NIVO: 3 mg/kg NIVO every 2 weeks ▪ 2L+ NIVO plus IPI: 3 mg/kg NIVO and 1 mg/kg IPI every 3 weeks for 4 doses, then 3 mg/kg NIVO every 2 weeks ▪ 1L NIVO plus IPI: 3 mg/kg NIVO every 2 weeks and 1 mg/kg IPI every 6 weeks Patients in all study cohorts were permitted to continue treatment beyond disease progression (as assessed by RECIST v1.1) if the patient tolerated the study drug and received clinical benefit as per investigator assessment. Dose interruptions were permitted for TRAEs, but dose modifications were not allowed.[5,6]
Comparator(s)	Cohorts in CM 142 are not randomised and are not intended to be formally compared with each other.
Follow-up time	Median (range) follow-up (time from first dose to data cutoff on September 15, 2022) was 64.2 (59.4-68.9) months [7]

CM 142	NCT02060188
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary endpoints consisted of ORR as determined by investigator assessment. Secondary endpoints include DCR, DOR, PFS, OS, and safety. Tumour assessments were conducted using ComT or MRI, per RECIST v1.1. Evaluations were conducted at baseline, every 6 weeks after first dose for 24 weeks, and then every 12 weeks until disease progression or treatment discontinuation. Patients could continue treatment beyond progression if the patient experienced clinical benefit and tolerated the treatment, per investigator assessment[8] Endpoint included in this application is postprogression survival (i.e., the rate of patients transitioning from progressed disease to death) which is used in the CEM as data from CM 8HW are immature and unavailable.
Method of analysis	Exploratory analyses for efficacy were conducted across defined subgroups including age, sex, ECOG PS, and KRAS and BRAF mutation status. Safety was assessed continually while patients were on treatment and for ≥ 100 days after discontinuation using National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.[8] The Kaplan-Meier product-limit method was used for median DOR, PFS, and OS determination; corresponding 95% CIs were calculated using log-log transformation. All *P* values were two-sided. Patient characteristics and safety data were summarised using descriptive statistics.[6]
Subgroup analyses	ORR was evaluated by patient characteristics subgroups including primary tumour location and BRAF or KRAS mutation status. PFS by BRAF or KRAS mutation status and outcomes among patients who discontinued therapy and did not receive subsequent therapy(treatment-free) were analysed post hoc [6]
Other relevant information	CM 142 is only provided as supportive information for the CEM as it was not designed or powered to measure the comparative efficacy of NIVO+IPI in this setting.

1L = first line; 2L = second line; BRAF serine/threonine-protein kinase B-Raf; ComT = computed tomography; CTLA-4 = Cytotoxic T-Cell Lymphoma-4 Antigen; DCR = disease control rate; DOR = duration of response; dMMR = Mismatch Repair Deficient; ECOG PS = Eastern Cooperative Oncology Group performance status; KRAS = Kirsten rat sarcoma viral oncogene; mCRC = metastatic colorectal cancer; MSI-H = Microsatellite Instability High; ORR = objective response rate; OS = overall survival; PD = Programmed Death Receptor; PD-L1 = Programmed Death Receptor -Ligand 1; PD-L2 = Programmed Death Receptor -Ligand 12; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours.

Sources: Lenz et al. (2024)[7]; Overman et al. (2022)[8]; Andre et al. (2022)[5]; Lenz et al. (2022)[6]

Table 3. Main characteristics of KN-177

KN-177	NCT02563002
Objective	To evaluate the efficacy and safety of PD-1 blockade with PEMBRO as compared with standard-of-care chemotherapy as first-line treatment in patients with MSI-H/dMMR mCRC
Publications – title, author, journal, year	▪ Shiu KK, André T, Kim TW, et al. LBA32 Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomized phase III KEYNOTE-177 study. Annals of Oncology, Volume 34, Supplement 2, 2023, Pages S1271-S1272,ISSN 0923-7534, https://doi.org/10.1016/j.annonc.2023.10.024. ▪ Diaz LA Jr, Shiu KK, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2022 May;23(5):659-670. doi: 10.1016/S1470-2045(22)00197-8. ▪ Andre T, Shiu KK, Kim TW, et al. Final overall survival for the phase III KN177 study: Pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). Journal of Clinical Oncology. 2021, 39(15_suppl), 3500-3500. https://doi.org/10.1200/JCO.2021.39.15_suppl.3500 ▪ André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med. 2020 Dec 3;383(23):2207-2218. doi: 10.1056/NEJMoa2017699.
Study type and design	A phase 3, open-label study of PEMBRO versus investigator-choice of chemotherapy in patients with previously untreated MSI-H/dMMR mCRC. Patients were randomly assigned in a 1:1 ratio to receive PEMBRO or chemotherapy (5-FU–based therapy with or without bevacizumab or cetuximab).
Sample size (n)	▪ 307 patients with MSI-H/dMMR mCRC without previous treatment who were randomly assigned to PEMBRO (n = 153) or chemotherapy (n = 154)
Main inclusion criteria	▪ Locally confirmed dMMR or MSI-H stage IV CRC ▪ ECOG performance status of 0 or 1 within 10 days prior to study start ▪ Life expectancy of at least 3 months ▪ Measurable disease ▪ Adequate organ function
Main exclusion criteria	▪ Has received prior systemic therapy for Stage IV CRC. May have received prior adjuvant chemotherapy for CRC as long as it was completed at least 6 months prior to randomisation on this study ▪ Currently participating and receiving treatment in another study, or participated in a study of an investigational agent and received treatment, or used an investigational device within 4 weeks of randomisation ▪ Known active central nervous system (CNS) metastases and/or carcinomatous meningitis ▪ Has received prior therapy with an immune checkpoint inhibitor (e.g., anti-PD-1, anti-PD L1, anti-PD-L2 agent, or anti- CTLA-4 agent, etc.)

KN-177	NCT02563002
Intervention	▪ PEMBRO 200 mg every 3 weeks.
Comparator(s)	▪ Investigator's choice of chemotherapy with intravenous mFOLFOX6 (oxaliplatin 85 mg/m² on day 1, leucovorin 400 mg/m² on day 1, and fluorouracil 400 mg/m² bolus on day 1 followed by a continuous infusion of 1200 mg/m² per day for 2 days on days 1-2) every 2 weeks; or intravenous FOLFIRI (irinotecan 180 mg/m² on day 1, leucovorin 400 mg/m² on day 1, and fluorouracil 400 mg/m² bolus on day 1 followed by a continuous infusion of 1200 mg/m² per day for 2 days on days 1-2), every 2 weeks, with or without intravenous bevacizumab (5 mg/kg on day 1) every 2 weeks or intravenous cetuximab (400 mg/m² in week 1 followed by 250 mg/m² weekly thereafter) ▪ Dose modifications for all chemotherapy drugs, bevacizumab, and cetuximab were permitted on the basis of toxic effects only and had to follow local guidelines. ▪ Oxaliplatin could be interrupted to prevent neuropathy and had to be resumed after 12 cycles of leucovorin and fluorouracil. ▪ Dose interruption and discontinuation, but not reduction, were permitted for PEMBRO to manage adverse events as described in the protocol.[9]
Follow-up time	▪ Median (range) study follow-up was 44.5 months (36.0-60.3) with PEMBRO vs. 44.4 months (36.2-58.6) with chemotherapy (final analysis based on data cutoff on Feb 19, 2021)[9] ▪ Median follow-up duration was 73.3 months (6.1 years; range, 64.9-89.2 months) at data cutoff July 17, 2023[10]
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	▪ The dual primary endpoints PFS per RECIST (version 1.1) by central review (defined as the time from randomisation to first disease progression or death from any cause) and OS (time from randomisation to death from any cause) in the ITT population. ▪ Secondary endpoints were ORR; the proportion of patients with complete and partial responses) per RECIST (version 1.1) by central review in the ITT population and safety and tolerability in all treated patients. ▪ Exploratory endpoints included PFS 2 (time from randomisation to progression or death from any cause on next line of therapy), PFS per immune-related RECIST by central review, duration of response (time from first complete or partial response until first disease progression or death from any cause) per RECIST (version 1.1) by central review, and health-related QoL using EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D-3L scales.[9,11]
Method of analysis	▪ The protocol specified two interim analyses and a final analysis. The proportional hazards assumption for OS was examined by both graphical and analytical methods. Adjustment for the effect of crossover on OS was done as a sensitivity analysis. ▪ The primary hypotheses that PEMBRO improves PFS and OS versus standard-of-care chemotherapies were assessed using a log-rank test. HRs were estimated with a Cox regression model and event rates over time were estimated using the Kaplan-Meier method. The ORR analysis was

KN-177	NCT02563002
	done only if the progression-free survival and overall survival null hypotheses were rejected. ▪ OS, PFS, ORR, and duration of response were assessed in the ITT population. ▪ Safety analyses were done including all patients who were randomly assigned and received at least one dose of study treatment[9]
Subgroup analyses	▪ Prespecified subgroup categories for the OS analysis were age, geographical region, recurrent versus newly diagnosed cancer, BRAF mutation status (wild-type versus $BRAFV^{600}E$ mutated), site of the primary tumour, hepatic or pulmonary metastases versus other metastases, and surgical versus non-surgical patients. ▪ Post hoc subgroups were sex, ECOG performance status, and KRAS or NRAS mutation status. ▪ The hazard ratios for death for the comparison of PEMBRO versus standard-of-care therapy in all subgroups were calculated with a Cox proportional regression model with Efron's method of tie handling with treatment as a covariate[9]
Other relevant information	

BRAF = serine/threonine-protein kinase B-Raf; CTLA-4 = Cytotoxic T-Cell Lymphoma-4 Antigen; dMMR = Mismatch Repair Deficient; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-CR29 = EORTC Quality of Life Questionnaire-Colorectal 29; FOLFIRI = 5-fluorouracil + leucovorin + irinotecan; FOLFOX = 5-fluorouracil + leucovorin + oxaliplatin; FU = fluorouracil; HIV = human immunodeficiency virus; ITT = intention to treat; KRAS = Kirsten rat sarcoma viral oncogene; mCRC = metastatic colorectal cancer; MSI-H = Microsatellite Instability High; NRAS = neuroblastoma rat sarcoma viral oncogene; ORR = objective response rate; OS = overall survival; PD = Programmed Death Receptor; PD-L1 = Programmed Death Receptor - Ligand 1; PD-L2 = Programmed Death Receptor-Ligand 2; PFS = progression-free survival; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumours.

Sources: Diaz et al. (2022)[9]; Shiu et al. (2023)[10]

Appendix B. Efficacy results per study

B.1 Results per study

Table 4. Results for CM 8HW: NIVO+IPI versus chemotherapy comparison (NCT04008030)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS	NIVO+IPI	[redacted]	[redacted]	—	—	—	[redacted]	[redacted]	NA	Per BICR in locally confirmed population. Stratified Cox proportional hazard model (at median follow-up of 31.51 months).	BMS data on file (2024)[12]
	Chemo	[redacted]	[redacted]								
GHS/QoL	NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			Summary of treatment difference (LS Mean change from baseline) at week 21. Continuous outcomes are compared between intervention groups using a standardised mean difference (i.e., effect size)[13]	BMS data on file (2024)[14]
	Chemo	[redacted]	[redacted]								
EQ-5D VAS	NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			Summary of treatment difference (LS Mean change from baseline) at week 21. Continuous outcomes are compared between intervention groups using a standardised mean difference (i.e., effect size)[13]	BMS data on file (2024)[14]
	Chemo	[redacted]	[redacted]								

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
EQ-5D utility index	NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			Summary of treatment difference (LS Mean change from baseline) at week 21. Continuous outcomes are compared between intervention groups using a standardised mean difference (i.e., effect size)[13]	BMS data on file (2024)[14]
	Chemo	[redacted]	[redacted]								

Table 5. Results for KN-177 (NCT02563002)

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS	PEMBRO	94/153	16.5 (5.4-38.1) months	—	—	—	0.60	0.45-0.79	NA	Per BICR in locally confirmed population. Cox regression model (at median follow-up of 73.3 months).	Shiu et al. (2023)[15]
	Chemo	122/154	8.2 (6.2-10.3) months								
GHS/QoL	PEMBRO	151	3.33 (−0.05 to 6.72)	8.96	4.24-13.69	0.0002	Effect size: 0.41			Summary of treatment difference (LS Mean) at week 21. Continuous outcomes are compared between intervention groups using a standardised mean difference (i.e., effect size)[13]	Andre et al. (2021)[11]
	Chemo	141	−5.63 (−9.32 to −1.94)								
EQ-5D VAS	PEMBRO	151	4.50 (1.16 to 7.83)	7.38	2.82-11.93	0.0016	Effect size: 0.35			Summary of treatment difference (LS Mean) at week 21. Continuous outcomes are compared between intervention groups using a standardised mean difference (i.e., effect size)[13]	Andre et al. (2021)[11]
	Chemo	141	−2.88 (−6.46 to 0.69)								

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
EQ-5D utility index	PEMBRO	151	0.04 (0.00-0.08)	0.05	0.00-0.10	0.031	Effect size: 0.21			Summary of treatment difference (LS Mean) at week 21. Continuous outcomes are compared between intervention groups using a standardised mean difference (i.e., effect size)[13]	Andre et al. (2021)[11]
	Chemo	141	−0.01 (−0.05 to 0.02)								

Appendix C. Comparative analysis of efficacy

As no meta-analysis was used, Table 6 is not applicable.

Table 6. Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	**Difference**	**CI**	**P value**	**Difference**	**CI**	**P value**		
NA									

C.1 Methodology

See main dossier.

C.2 Data sources

C.2.1 CM 8HW data

The October 2023 database lock of the CM 8HW trial included data for 303 patients with 202 in the NIVO+IPI arm and 101 in chemotherapy arm. [redacted] The trial had a median overall follow-up of [redacted] The analyses were conducted on available IPD data.

C.2.2 KN-177 data

KN-177 input data was derived from published HR and PFS KM curves in Shiu et al. (2023)[10] with a 5-year follow-up. The KM curves were digitised to construct pseudo-IPD. Digitisation involved extracting graphed TTE curves by digitally approximating the published curves and subsequently correcting for any discrepancies in the approximation. Mapping the published KM survival curves to pseudo-IPD followed the methodology as described in Guyot et al. (2012).[16]

C.3 Statistical methods

C.3.1 (Anchored) MAIC methodology

MAIC is a population-adjusted treatment comparison method to adjust for cross-study differences in clinically relevant TEMs. 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 National Institute for Health and Care Excellence (NICE) DSU Technical Support Document 18.[17] The matching methodology is designed to statistically construct trial patient populations that are like one another so that the outcomes from the trials can be meaningfully compared.

Population adjustment is done using the IPD from one study to match the population of the other study. CM 8HW was matched to the pseudo-IPD from the KN-177 study by means of anchored MAIC. Anchored indirect comparisons between two treatments rely on the presence of a common comparator, in this case, the chemotherapy arms of both trials were used as a common comparator. Randomisation within each trial ensures bias due to imbalanced prognostic variables across the trials is omitted. TEMs (baseline characteristics that modify the effect of treatment) are not controlled for through randomisation and introduce bias in the estimated relative treatment effect should they

not be corrected for. Therefore, these TEMs are matched in the MAIC methodology. By matching on TEMs, the CM 8HW patient population is reweighted such that the resulting population aligns with KN-177 population with regards to the TEM distribution and their survival outcomes can be meaningfully compared.

C.3.2 Unanchored MAIC methodology

The unanchored MAIC methodology is similar to the methodology described above for the anchored analyses. However, there are two key distinctions, namely, while the anchored analyses matches the full trial population of interest (e.g., CM 8HW), the unanchored analyses matches only the intervention arm populations of interest (e.g., NIVO+IPI). Secondly, as randomisation is preserved in the anchored analyses via the common comparator only TEMs need to be accounted for in the matching. However, as randomisation is not persevered in the unanchored analyses, the unanchored analyses requires an adjustment for TEMs and prognostic variables. See appendix Section C.8.1.3 for the selection of additional prognostic variables for the unanchored analysis.

While both the anchored and unanchored analyses utilise a similar methodology, the subsequent sections primarily detail the methodology employed in the anchored analyses, which includes matching of, for instance, 'CM 8HW.' However, it is important to note that a comparable methodology has been implemented in the unanchored analyses, but with a key difference: the matching was conducted specifically for the NIVO+IPI arm.

C.3.3 Estimation of matching-adjusted indirect comparison weights

For the weighted analyses, inverse odds were estimated for each CM 8HW patient, representing the probability of the patient being part of KN-177. These odds were used as weights to create the matched population. The resulting weights were used to obtain statistically similar trial populations, after which survival outcomes can meaningfully be compared. Matching allowed these weights to be created simultaneously for many patient characteristics. The method for calculating these odds is called propensity score weighting. Effectively, patients who were more likely to be among the target aggregate population (given their characteristics) were assigned higher weights in the analysis and vice versa. Propensity score weights were estimated using logistic regression as:

$$\log(w_{it}) = a_0 + a_1^T X_{it}^{EM}$$

where X_{it}^{EM} is the effect modifier covariate vector for the i-th individual in CM 8HW study and w_{it} is the weight of the i-th individual.

As IPD was not available for KN-177, the weights cannot be estimated using standard logistic regression methods. Instead, the method of moments approach was used to estimate $\hat{a}_1$ so that the weights balance the mean covariate values between the populations of MAIC-reweighted CM 8HW and the KN-177 populations.

As the reweighting process results in a loss of statistical information, the effective sample size (ESS) of a reweighted population is lower than the total number of patients, and reweighting on a larger number of variables usually yields a larger reduction in ESS.

Therefore, careful selection of characteristics for matching is important to construct trial populations with sufficient clinical similarity to compare outcomes and sufficient sample sizes. Markedly reduced ESS may cause unstable outcome estimates and inferences would depend on a low number of individuals.[17] Although there is no standard threshold for a markedly reduced ESS, an ESS that is at least 43% of the initial sample size could still be considered acceptable.[17] The distribution of weights was assessed to check for patients with individual high weights which may have a disproportionate impact on the analysis results.

Relative treatment effects in terms of PFS of NIVO+IPI versus PEMBRO after matching were estimated using (time-varying) log HRs and their standard errors following NICE MAIC recommendations.[17]

C.3.4 Diagnostics of MAIC weights

The loss of statistical information in the reweighted trial data is reflected in the ESS being lower than the initial sample size of the CM 8HW trial. The ESS was estimated as:

$$\mathrm{ESS} = \frac{\left(\sum_{i=1}^{N} \hat{w}_i\right)^2}{\sum_{i=1}^{N} \hat{w}_i{}^2}$$

ESS is defined as "the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate."[17] A small ESS is indicative of highly variable weights due to lack of population overlap; as such, the estimates may be unstable.

To diagnose population overlap, the distribution of weights themselves was examined. Rescaled weights calculated using the following formula were presented in histograms:

$$\hat{\omega}_i = \frac{\hat{w}_i}{\sum_{i=1}^{N} \hat{w}_i} \times N$$

where N is the number of subjects in CM 8HW. Rescaled weights > 1 indicate that a patient carries more weight in the reweighted pseudo-population than the original trial sample, while a rescaled weight < 1 means that an individual carries less weight in the reweighted population than the original data.

C.3.5 Extrapolation of survival using parametric curves

As the PHA was violated for PFS in the KN-177 trial, CM 8HW trial, and between the NIVO+IPI and PEMBRO arms of the trials (see Section C.8.1.1), an ITC based on HR may be biased. To enable an ITC over the observed trial period, survival was extrapolated using parametric survival curves.

Independent standard parametric survival models were fitted to each treatment arm of both trials. The parametric distributions fitted to the trial were the exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull distributions. An overview of the parametric distributions, the survival function, and the main characteristic of these distributions is presented in Table 7. The table defines whether

the model is a PH or an AFT model. A PH model operates on the hazards scale, and the effect of determinants is proportional (multiplicative) on hazards. The treatment effect is expressed as a HR. For example, a HR of 1.5 increases the hazard function by a factor of 1.5. An AFT model operates on the time scale, and the effect of determinants is proportional (multiplicative) on survival time. Treatment effect is expressed as an acceleration factor, which either accelerates or delays the time to an event. If a coefficient of the treatment (on the log scale) is log (2), then applying treatment versus no treatment would give half the expected survival time.

Age-dependent and sex-stratified background mortality was included in the fitted survival models based on the most up-to-date UK life tables published by the Office for National Statistics (ONS), 2018-2020. The propensity score weights derived from the MAIC were included in the analysis for CM 8HW/NIVO+IPI data in the anchored and unanchored analyses, respectively.

Table 7. Parametric distribution

Parametric distribution	Survival function	Notation	Main characteristics
Exponential	$S(t) = \exp(-\lambda t)$	▪ λ rate ▪ t time	▪ PH model ▪ Constant hazard ▪ 1 parameter
Weibull	$S(t) = \exp\left(-\left(\frac{t}{\lambda}\right)^{p}\right)$	▪ λ scale parameter ▪ P shape parameter	▪ AFT model ▪ Either increase or decrease monotonically ▪ 2 parameters
Gompertz	$S(t) = \exp\left(\left(\frac{\lambda}{p}\right)(1-e^{pt})\right)$	▪ λ scale parameter ▪ P shape parameter	▪ PH model ▪ Either increase or decrease monotonically ▪ 2 parameters
Log-Normal	$S(t) = 1 - \Phi\left(\frac{\ln(t) - \mu}{\sigma}\right)$	▪ Φ standard normal function ▪ μ meanlog ▪ σ sdlog	▪ AFT model ▪ Hazard increases initially to a maximum, before decreasing as t increases ▪ 2 parameters
Log-logistic	$S(t) = \frac{1}{1+\left(\frac{t}{\lambda}\right)^{p}}$	▪ λ scale parameter ▪ P shape parameter	▪ AFT model ▪ Can be non-monotonic with respect to time ▪ 2 parameters
Gamma	$S(t) = 1 - \frac{\gamma(k,\lambda t)}{\Gamma(k)}$ $\gamma(k,x) = \int_0^x \lambda^{k-1} e^{-x} dx$	▪ λ rate parameter ▪ k shape parameter ▪ $\gamma(k,x)$ lower incomplete Gamma function	▪ AFT model ▪ Either increase or decrease monotonically ▪ 2 parameters

Parametric distribution	Survival function	Notation	Main characteristics
Generalised gamma	$1 - S_G\left(\frac{\exp(Qw)}{Q^2}\middle\vert\frac{1}{Q^2},1\right), Q < 0$ $S_G\left(\frac{\exp(Qw)}{Q^2}\middle\vert\frac{1}{Q^2},1\right), Q > 0$ $1 - S_L(t\vert\mu,\sigma), Q = 0$	▪ μ location parameter ▪ $\sigma < 0$ scale parameter ▪ Q shape parameter ▪ $S_L(t\vert\mu,\sigma)$ survival function of the Log-normal distribution with log mean μ and log sd σ ▪ $S_G(t\vert a,1)$ Survival function of the Gamma distribution with shape a and scale 1	▪ AFT model ▪ 3 parameters ▪ Exponential, Weibull and Gamma distributions are special cases of this distribution.

AFT = accelerated failure time; PH = proportional hazards.

C.3.5.1 Model selection

The selection of extrapolation models was based on statistical fit of the models to the trial data, based on AIC score and BIC score, as well as visual inspection of the survival curves and hazard plots.

C.3.5.1.1 Statistical fit criteria

Model selection based on statistical model fit was based on the AIC and BIC scores for the models. Both the AIC and BIC scores assess goodness of fit using a log-likelihood function. While the AIC penalises a model only for additional and potentially inefficient additional parameters, the BIC score also considers the sample size (number of observations).

$$AIC = -2 * loglikelihood + 2 * number\ of\ estimated\ parameters$$

$$BIC = -2 * loglikelihood + \ln(\text{number of observations}) * (number\ of\ estimated\ parameters)$$

As the BIC is more stringent toward both type I and type II errors, it can potentially protect against overfitting. It should be noted that AIC and BIC scores can only be compared when models are fit to the same set of data.

When comparing AIC and BIC values between models, aside from selecting the model with the best statistical fit criteria (i.e., the one with the lowest value), it is important to know which distribution is second-best, as well as some measure of its standing with respect to the best model. Table 8 gives an overview of how the difference in AIC and BIC scores across models fit to a set of data should be interpreted. Differences in AIC values of ≤ 2 indicate that there is substantial support of evidence that the two compared

models have the same merits. Differences in BIC values between 0-2 indicate weak evidence of difference between the two compared models.

Table 8. Interpretation of AIC and BIC differences

AIC difference: Burnham and Anderson (2004)[18]			BIC difference: Raftery (1995)[19]		
AIC difference		**Evidence**	**BIC difference**		**Evidence of difference**
	≤ 2	Substantial support		0-2	Weak
	2 < Δ < 4			2-6	Positive
	4 ≤ Δ ≤ 7	Considerably less support		6-10	Strong
	4 < Δ ≤ 10			> 10	Very strong
	Δ > 10	Essentially no support			

AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion

C.3.5.1.2 Visual inspection of extrapolation curves

Models were also assessed based on the visual fit following the recommendations in the NICE DSU Technical Support Document 14.[20] It should be noted that this method was used with caution and only complementary to the other model selection methods. Due to censoring and clustered data points in the KM curve, some parts of the extrapolated curve may fit the observed data very well, while in other parts it may not. This does not necessarily mean that the model is inappropriate. Furthermore, if the parametric curves closely follow the observed data, this does not necessarily mean that they are able to correctly predict survival beyond the trial duration, especially at the tail of the curve.

C.3.5.1.3 Visual inspection of smoothed hazard curves

In addition to visual assessment of the extrapolation curves, a visual assessment of the smoothed hazard curves was performed. The smoothed hazard curve indicates whether observed hazards are likely to be constant, monotonic or non-monotonic. In general, the hazards of the exponential models provide the best fit when the observed hazard is approximately constant and non-zero. The Weibull and Gompertz models incorporate monotonic hazards, while the log-logistic and log-normal models can incorporate non-monotonic hazards. The generalised gamma is generally more flexible in incorporating multiple turning points in hazards. This is because the generalised gamma model has three parameters. As with the visual inspection of extrapolation curves (and other validation criteria), the observed smoothed hazard curves do not always predict the hazards beyond the trial period.

As per NICE recommendation,[20] the same fitted distribution is used to model both arms of a trial. This ensures that relative efficacy is not influenced by the choice/attributes of different curves.

C.3.6 Estimation of time-varying HRs based on parametric survival extrapolations

C.3.6.1 Anchored analysis

As the PHA was not held, the extrapolation of a constant HR between NIVO+IPI vs. PEMBRO beyond the observed period may be biased. To circumvent this limitation, time-varying hazards based on the predicted hazards from the best-fitting survival curves for each trial were used to estimate hazard ratios for NIVO+IPI vs. PEMBRO for each timepoint in the extrapolation. The predicted hazards for each treatment arm based on the best-fitting survival distribution were generated using predict function in R for each timepoint till the end of the extrapolation. Hazard ratios within each trial were calculated by dividing the hazard for the treatment arm by the hazard for the comparator arm. The 95% confidence level was calculated using the delta method, as provided in the formula below.

The hazard ratio between NIVO+IPI vs. PEMBRO for each timepoint was calculated using the Bucher method,[21] with the 95% confidence intervals based on variances derived using the delta method as shown below.

$$HR_{\text{NIVO+IPI vs. PEMBRO}} = (Hazard_{\text{NIVO+IPI}} / Hazard_{\text{Chemotherapy (CM 8HW)}}) / (Hazard_{\text{PEMBRO}} / Hazard_{\text{Chemotherapy (KN-177)}})$$

Using the Delta method,

$$\text{Variance of } HR_{\text{NIVO+IPI vs. PEMBRO}} = (\text{SE of } Hazard_{\text{NIVO+IPI}} / Hazard_{\text{NIVO+IPI}})^2 +$$

$$(\text{SE of } Hazard_{\text{Chemotherapy (CM 8HW)}} / Hazard_{\text{Chemotherapy (CM 8HW)}})^2 +$$

$$(\text{SE of } Hazard_{\text{PEMBRO}} / Hazard_{\text{PEMBRO}})^2 +$$

$$(\text{SE of } Hazard_{\text{Chemotherapy (KN-177)}} / Hazard_{\text{Chemotherapy (KN-177)}})^2$$

$$95\%\ CI = \exp(\log HR_{\text{NIVO+IPI vs. PEMBRO}} +/- (1.96 * \text{sqrt}(\text{Variance of } HR_{\text{NIVO+IPI vs. PEMBRO}})))$$

C.3.6.2 Unanchored analysis

Similarly, the PHA was not held in the unanchored analysis and the extrapolation of a constant HR between NIVO+IPI vs. PEMBRO beyond the observed period may be biased. To circumvent this limitation, time-varying hazards based on the predicted hazards from the best-fitting survival curves for both arms were used to estimate hazard ratios for NIVO+IPI vs. PEMBRO for each timepoint in the extrapolation. The predicted hazards for each treatment arm based on the best-fitting survival distribution were generated using predict function in R for each timepoint till the end of the extrapolation. Hazard ratios were calculated by dividing the hazard for NIVO +IPI by the hazard of PEMBRO. The 95% confidence level was calculated using the delta method, as provided in the formula below.

$$HR_{\text{NIVO+IPI vs. PEMBRO}} = Hazard_{\text{NIVO+IPI}} / Hazard_{\text{PEMBRO}}$$

Using the Delta method,

$$\text{Variance of } HR_{\text{NIVO+IPI vs. PEMBRO}} = (\text{SE of } \text{Hazard}_{\text{NIVO+IPI}} / \text{Hazard}_{\text{NIVO+IPI}})^2 +$$

$$(\text{SE of } \text{Hazard}_{\text{PEMBRO}} / \text{Hazard}_{\text{PEMBRO}})^2$$

$$95\%\ CI = \exp(HR_{\text{NIVO+IPI vs. PEMBRO}} +/- (1.96 * \text{sqrt}(\text{Variance of } HR_{\text{NIVO+IPI vs. PEMBRO}})))$$

C.3.6.3 Constant hazard ratio-based network meta-analysis

The second methodology employed for the anchored ITC was an HR-based NMA. As the unanchored analysis lacks a common comparator, the comparative estimate for the unanchored analyses is derived solely from a Cox HR (95% CI), which is based on the IPD and pseudo-IPD from NIVO+IPI and PEMBRO.

C.3.6.4 Fixed-effects model

The study used a fixed-effects meta-analysis due to the limited evidence network.

A fixed-effects model, for a simplified case of two treatment arms, comparing treatment A and treatment B, can be expressed in the following equations:

$$\eta_{jk} = \begin{cases} \mu_j, k = A \\ \mu_j + d, k = B \end{cases}$$

η_{jk} is the underlying outcome for treatment k in study j, μ_j the outcome for treatment A in study j and d the effect of treatment B relative to treatment A. The treatment effect, d, is assumed to be equal for all studies. On the other hand, the treatment effect differs by trial in the random-effects model. The treatment effect is typically assumed to be normally distributed with a certain mean and variance.

$$\eta_{jk} = \begin{cases} \mu_j, k = A \\ \mu_j + \delta, k = B \end{cases}$$

$$\delta \sim \mathcal{N}(d, \sigma^2)$$

C.3.6.5 Bayesian HR-based NMA framework

The NMA was conducted in a Bayesian framework, which makes the selection of priors important, as they display prior beliefs of the distribution of parameters. The use of informative priors may be an alternative to non-informative priors, but this approach requires informed prior knowledge, which was unavailable in the context of this study in 1L MSI-H/dMMR mCRC. Within this study, a non-informative prior was employed. For the treatment effect (log HR), a normal distribution with mean 0 and precision 0.0001 will be used. Consequently, the prior treats all therapies equally, and the difference in the estimated treatment effect comes predominantly from observed data.

The analyses were performed using the R interface to Stan (the package RStan) and using the multinma package developed by Phillipo (2020)[22] that implements NMA models to combine evidence from a network of studies and treatments using aggregate data from

studies included. The continuous outcome analysed in the NMA, namely the HR of PFS, was analysed using a fixed-effects generalised linear model as described in the NICE DSU TSD 2 (see Program 7 in Dias et al.). It was assumed that the data came from a normal likelihood and modelled the HR of a given treatment in a specified trial in a linear regression model. The relative effect of each treatment comparison was expressed as the HR. Additionally, pairwise comparisons were conducted between all treatments of interest.

In the Monte Carlo simulation, four simulation chains were used with 5000 iterations, including 2500 burn-in (also known as warm-up), for each model that was run. One primary advantage of using Stan over other Bayesian software (such as WinBUGS and JAGS), is that the sampling method, Hamiltonian Monte Carlo is much more efficient in sampling from the relevant posterior space in comparison to the Gibbs sampling method used in WinBUGS. Therefore, we require fewer iterations from the model to gain a good understanding of the posterior distribution for the model parameters. The Gelman-Rubin statistics, the size of the Monte Carlo error, the auto-correlation function, trace plots, and Kernel density plots were examined to assess the convergence.

C.4 Results

The following sections display the results of the population-adjusted anchored ITC, Section C.4.1 provides an overview of the population matching, Section C.4.2 details the results of the time-varying HR analyses, and Section C.5 includes the constant HR-based NMA scenario analysis results. Scenario analyses conducted on unweighted CM 8HW data can be found in Section C.8.2. Furthermore, the unanchored analyses results can be found in Section C.6.

C.4.1 Matching CM 8HW to KN-177

[redacted] The propensity score weights ranged from [redacted] indicating no extreme weights being generated. A summary of the weights and their histogram are in Table 9 and Figure 1.

Figure 1. Distribution of propensity score weights for CM 8HW matched to KN-177

Table 9. Summary of propensity score weights for CM 8HW

Min	Median	Mean	Max
[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics before and after matching for CM 8HW to KN-177 are provided in Table 10. Most TEMs 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 in in CM 8HW and more patients from the rest of the world as 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 10. Summary of patient characteristics included in the MAIC – CM 8HW and KN-177 populations

Identified TEMs	KN-177 (N = 307)	CM 8HW (N = 303) unadjusted	CM 8HW (N = 241.7) matched
Age, in years [median, range]	63 (24-93)	[redacted]	[redacted]

Identified TEMs	KN-177 (N = 307)	CM 8HW (N = 303) unadjusted	CM 8HW (N = 241.7) matched
ECOG performance status 0	159 (52%)	[redacted]	[redacted]
BRAF/KRAS/NRAS mutation status			
BRAF, KRAS, NRAS all wild-type	69 (22%)	[redacted]	[redacted]
KRAS or NRAS mutant*	74 (24%)	[redacted]	[redacted]
BRAF mutant*	77 (25%)	[redacted]	[redacted]
Could not be evaluated	90 (29%)	[redacted]	[redacted]
Site of primary tumour (sidedness)			
Right	219 (71%)[$]	[redacted]	[redacted]
Left	88 (29%)	[redacted]	[redacted]
Liver metastasis	125 (41%)	[redacted]	[redacted]
Liver or lung metastasis	159 (52%)	[redacted]	[redacted]
Region			
Asia	48 (16%)	[redacted]	[redacted]
Western Europe/North America**	222 (72%)	[redacted]	[redacted]
Rest of the world	37 (12%)	[redacted]	[redacted]

* Three patients from KN-177 and seven patients from CM 8HW 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'; **CM 8HW reported 'US/Canada/Europe' patients from Czech Republic and Romania were reclassified to the rest of the world.

N: Number of subjects in the unadjusted analysis set; ESS: Effective sample size of the weighted analysis set.

When comparing the weighted and unweighted KM curves, weighting did not change the survival estimates significantly, see Figure 2. [redacted] Figure 2 and Table 11 show the KM curves, and HRs with 95% CI for CM 8HW before and after matching, respectively.

Figure 2. Kaplan-Meier plots of CM 8HW before and after matching

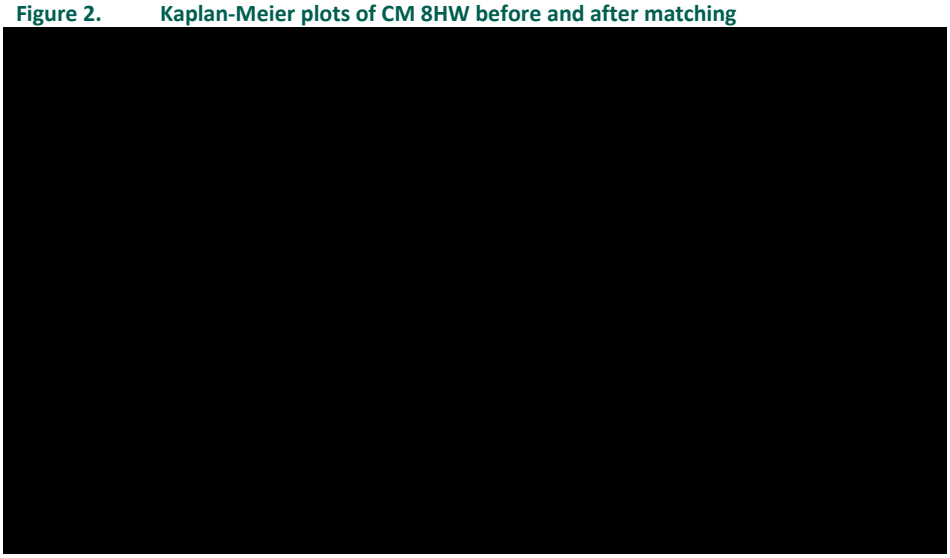


Table 11. HRs and 95% CI for CM 8HW before and after matching

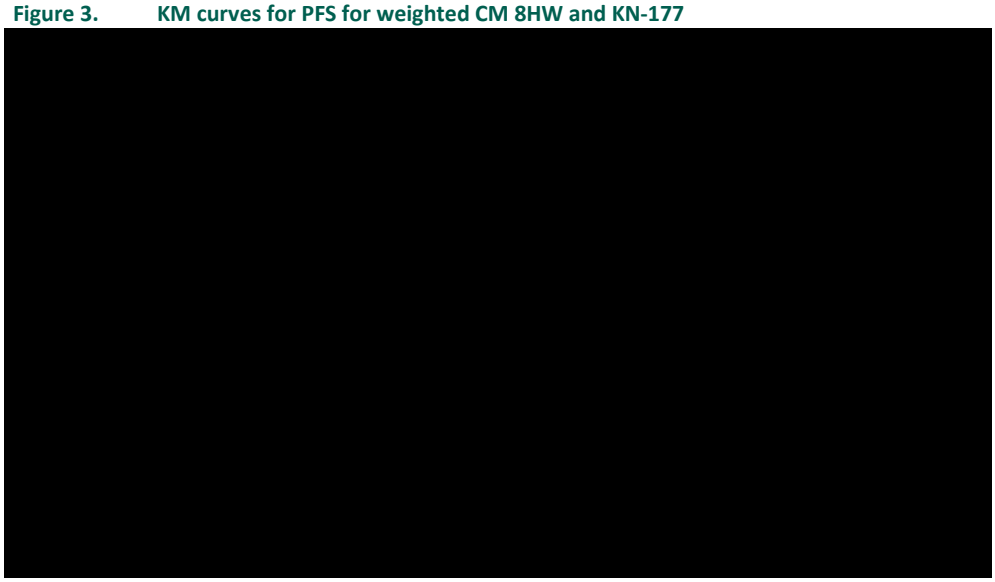
CM 8HW (NIVO+IPI vs. Chemo)	HR (95% CI))
[redacted]	[redacted]
[redacted]	[redacted]

C.4.2 ITC of NIVO+IPI vs. PEMBRO based on Time-varying HRs

C.4.2.1 Survival in weighted CM 8HW and KN-177

The PFS KM curves for matched CM 8HW and KN-177 are shown in Figure 3. [redacted]

Figure 3. KM curves for PFS for weighted CM 8HW and KN-177



As the PHA is violated for KN-177 PFS data, seven independent parametric survival distributions were fit to NIVO+IPI, PEMBRO, and the chemotherapy arms of weighted CM 8HW data and KN-177 based on the methods described in the Section C.3.5. The results from the survival curve fitting and selection of best-fitting distribution for each trial are detailed below. Please note, that to avoid that relative efficacy is influenced by the choice/attributes of different distributions, a common distribution for each arm in the trial was selected.

C.4.2.1.1 Weighted CM 8HW

From the seven parametric survival distributions fitted to both arms, [redacted] had the lowest AIC and BIC in the NIVO+IPI arm (Table 12). [redacted]

Table 12. Statistical fit – weighted CM 8HW

	NIVO + IPO		Chemotherapy		Combined	
Distribution	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Distribution	NIVO + IPO		Chemotherapy		Combined	
	AIC	BIC	AIC	BIC	AIC	BIC
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values within < 2 (total combined column values < 4) from the best-fitting AIC/BIC are shaded pink.

AIC: Akaike inf Akaike information criteria; BIC: Bayesian information criteria; A difference of < 2 units for AIC or BIC is not considered meaningful.

Based on the visual assessment of fit, all except exponential distribution showed acceptable fit to the observed data in the NIVO+IPI arm with [redacted] appearing to follow the observed data the best (Figure 4). [redacted], with [redacted] appearing to represent the observed data better (Figure 5).

Figure 4. Observed KM curve and fitted parametric distributions for NIVO+IPI – weighted CM 8HW.

[redacted]

Figure 5. Observed KM curve and fitted parametric distributions for chemotherapy – weighted CM 8HW

On long-term extrapolations (Section C.8.1.4), exponential showed [redacted] All curves predicted 100% mortality by approximately [redacted]

Based on the visual assessment of fit and statistical fits of the parametric survival models, [redacted] The predicted PFS for the NIVO+IPI arm [redacted] in first-line mCRC patients in the CM 142 trial. While the predicted 5-year PFS for chemotherapy is [redacted] than the 7.6% published 5-year survival data observed in KN-177 for chemotherapy.[10]

C.4.2.1.2 KN-177

From the seven parametric survival distributions fitted to both arms, [redacted]

Table 13. Statistical fit – KN-177

	PEMBRO		Chemotherapy		Combined	
Distribution	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]					
Gamma	[redacted]					
Generalised gamma	[redacted]					
Gompertz	[redacted]					
Log-logistic	[redacted]					
Log-normal	[redacted]					
Weibull	[redacted]					

Values within < 2 (total combined column values < 4) from the best-fitting AIC/BIC are shaded pink.

AIC: Akaike inf Akaike information criteria; BIC: Bayesian information criteria; A difference of < 2 units for AIC or BIC is not considered meaningful.

Based on the visual assessment of fit, [redacted] (Figure 7).

Figure 6. Observed KM curve and fitted parametric distributions for PEMBRO – KN-177

[redacted]

Figure 7. Observed KM curve and fitted parametric distributions for chemotherapy – KN-177

On long-term extrapolations (Section C.8.1.4),

Based on the visual assessment of fit and statistical fits of the parametric survival models, the published 5-year survival data (34.0% and 7.6% for PEMBRO and chemotherapy, respectively).[10]

C.4.2.1.3 Extrapolated survival in weighted CM 8HW and KN-177

The PFS KM curves for weighted CM 8HW and KN-177, as well as the long-term extrapolation based on the best-fitting distribution are shown in Figure 8.

Figure 8. PFS KM curves and extrapolated best-fitting distributions

C.4.2.2 Estimated time-varying HRs

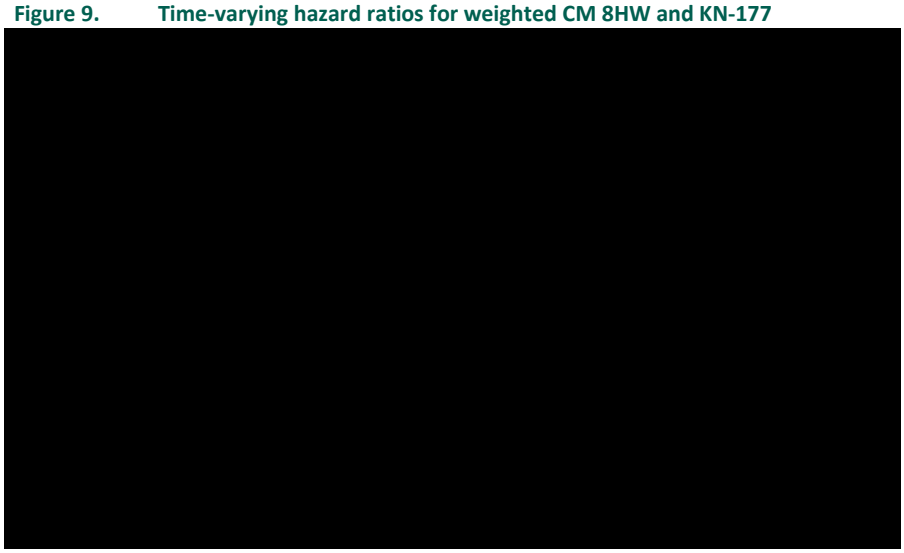
The parametric distributions were used to generate the time-varying HRs. In the first step, the within-trial time-varying HRs of NIVO+IPI vs. chemotherapy and PEMBRO vs. chemotherapy were estimated. Secondly, these were then used to derive the time-varying HR of NIVO+IPI vs. PEMBRO.

C.4.2.2.1 Estimated within-trial time-varying hazard ratio

The fitted parametric distributions were utilised to estimate hazards and their standard errors over time. Based on these, time-varying hazard ratios for each timepoint of the extrapolation were estimated along with their 95% CIs, as described in Section C.3.6. These estimated time-varying PFS HRs per trial are shown in Figure 9.

The time-varying HRs for both trials [redacted] The HR for weighted CM 8HW reaches a minimum of approximately [redacted] The HR for KN-177 also reaches its minimum of approximately [redacted]. The HRs for both trials are seen to be steadily [redacted] The 95% CIs around the HRs are [redacted]

Figure 9. Time-varying hazard ratios for weighted CM 8HW and KN-177

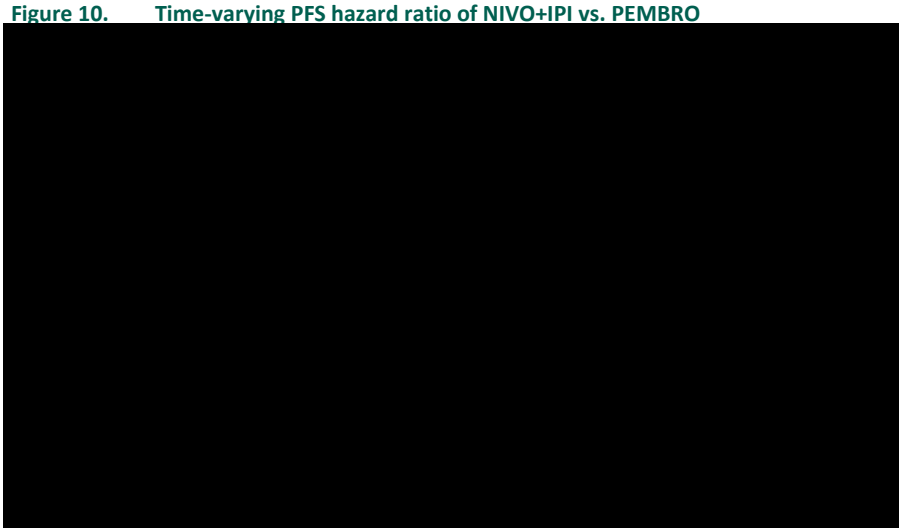


C.4.2.2.2 Time-varying hazard ratio: NIVO+IPI vs. PEMBRO

The PFS time-varying hazard ratio for NIVO+IPI vs. PEMBRO and its 95% CIs were estimated using the Bucher ITC approach based on the derived within-trial time-varying HRs, as described in Section C.3.6.

The estimated time-varying PFS HR for NIVO+IPI vs. PEMBRO is shown in Figure 10, and Table 14 provides point estimates for yearly intervals. The point estimate of the time-varying HR is

Figure 10. Time-varying PFS hazard ratio of NIVO+IPI vs. PEMBRO



Please note, that the green dotted line in the figure represents the estimated HR for NIVO+IPI vs. PEMBRO based on the constant HR approach used in the scenario analysis.

Table 14. Time-varying PFS HRs for NIVO+IPI vs. PEMBRO in 12-month intervals

Time (in months)	HR (95% CI)
0	[redacted]
12	[redacted]
24	[redacted]
36	[redacted]
48	[redacted]
60	[redacted]
72	[redacted]
84	[redacted]
96	[redacted]
108	[redacted]
120	[redacted]

C.5 Scenario analysis: ITC of NIVO+IPI vs. PEMBRO based on a constant hazard ratio-based NMA

An HR-based NMA was performed as a scenario analysis based on the methods described in Section C.3. As the PHA was violated, the results from this method may be biased and should be interpreted with caution.

The analysis used published KN-177 PFS hazard ratios from 5-year follow-up data[10] [HR, 0.60 (0.45-0.79)] and [redacted] The fixed effect Bayesian HR-based NMA estimated [redacted] This is suggestive of a [redacted] in the studied population as the estimated [redacted] Table 15 shows the pairwise posterior estimates of HR and their 95% CrIs.

Table 15. Pairwise posterior estimates of hazard ratio and 95% credible intervals based on fixed effect Bayesian NMA

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

C.6 Unanchored analysis

C.6.1 Matching NIVO+IPI of CM 8HW to PEMBRO of KN-177

[redacted] matching the NIVO+IPI arm of CM 8HW to the KN-177 PEMBRO population. [redacted] The propensity score weights ranged from [redacted] A summary of the weights and their histogram are in Table 16 and Figure 11.

Figure 11. Distribution of propensity score weights for NIVO+IPI matched to PEMBRO

[redacted]

Table 16. Summary of propensity score weights for NIVO+IPI

Min	Median	Mean	Max
[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristics before and after matching for NIVO+IPI to PEMBRO are provided in Table 17. [redacted]

[redacted]

Table 17. Summary of patient characteristics included in the MAIC – NIVO+IPI and PEMBRO populations

Matching variables	PEMBRO (N = 153)	NIVO+IPI (N = 202) unadjusted	NIVO+IPI (N = 136.47) matched
Age, in years [median, range]	63 (24-93)	[redacted]	[redacted]
ECOG performance status 0	75 (49%)	[redacted]	[redacted]
BRAF/KRAS/NRAS mutation status			
BRAF, KRAS, NRAS all wild-type	34 (22%)	[redacted]	[redacted]
KRAS or NRAS mutant*	33 (22%)	[redacted]	[redacted]
BRAF mutant*	34 (22%)	[redacted]	[redacted]
Could not be evaluated	52 (34%)	[redacted]	[redacted]
Site of primary tumour (sidedness)			
Right	[$]107 (70%)	[redacted]	[redacted]
Left	46 (30%)	[redacted]	[redacted]
Liver metastasis	71 (46%)	[redacted]	[redacted]
Lung metastasis	36 (24%)	[redacted]	[redacted]
Region			
Asia	22 (14%)	[redacted]	[redacted]
Western Europe/North America**	109 (71%)	[redacted]	[redacted]
Rest of the world	22 (14%)	[redacted]	[redacted]
Prior chemotherapy (adjuvant or neoadjuvant)	38 (25%)	[redacted]	[redacted]
Synchronous/metachronous metastases			
Recurrent metachronous	80 (52%)	[redacted]	[redacted]

Matching variables	PEMBRO (N = 153)	NIVO+IPI (N = 202) unadjusted	NIVO+IPI (N = 136.47) matched
Newly diagnosed with metastatic disease	73 (48%)	[redacted]	[redacted]
Not reported/missing	0 (0%)	[redacted]	[redacted]

[$] Includes 5 patients who were classified 'both sided'; **CM 8HW reported 'US/Canada/Europe' patients from Czech Republic and Romania were reclassified to the rest of the world.

N: Number of subjects in the unadjusted analysis set; ESS: Effective sample size of the weighted analysis set.

When comparing the weighted and unweighted KM curves, [redacted] see Figure 12. The weighted and unweighted NIVO+IPI curves [redacted].

Furthermore, when comparing NIVO+IPI vs. PEMBRO via Cox HR, both the weighted and unweighted analyses indicated [redacted] Figure 12 and Table 18 show the KM curves, and HRs with 95% CI for NIVO+IPI vs. PEMBRO before and after matching, respectively.

Figure 12. Kaplan-Meier plots of NIVO+IPI of CM 8HW before and after matching and PEMBRO

[redacted]

Table 18. HRs and 95% CI for NIVO+IPI vs. PEMBRO before and after matching

NIVO+IPI vs. PEMBRO (Cox PH based)	Hazard ratio (95% CI)
Unweighted	[redacted]

NIVO+IPI vs. PEMBRO (Cox PH based)	Hazard ratio (95% CI)
Weighted to PEMBRO	[redacted]

C.6.2 ITC of NIVO+IPI vs. PEMBRO based on time-varying HRs

As the PHA is likely violated for the NIVO+IPI and PEMBRO PFS comparison, seven independent parametric survival distributions were fit to the weighted NIVO+IPI and PEMBRO based on the methods described in the Section C.3.5. The results from the survival curve fitting and selection of best-fitting distribution for each trial are detailed below. Please note, that to avoid that relative efficacy is influenced by the choice/attributes of different distributions, a common distribution for both arms was selected.

From the seven parametric survival distributions fitted to both arms, [redacted] respectively (Table 19) [redacted]

Table 19. Statistical fit – weighted NIVO+IPI and PEMBRO

	NIVO + IPO		PEMBRO		Combined	
Distribution	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]					
Gamma	[redacted]					
Generalised gamma	[redacted]					
Gompertz	[redacted]					
Log-logistic	[redacted]					
Log-normal	[redacted]					
Weibull	[redacted]					

Values within < 2 (total combined column values < 4) from the best-fitting AIC/BIC are shaded pink.

AIC: Akaike inf Akaike information criteria; BIC: Bayesian information criteria; A difference of < 2 units for AIC or BIC is not considered meaningful.

Based on the visual assessment of fit, [redacted] showed acceptable fit to the observed data in the NIVO+IPI arm [redacted] appearing to follow the observed data the best (Figure 13). [redacted] tracked the observed data quite well [redacted]

[redacted] appearing to represent the observed data best [redacted]

Figure 13. Observed KM curve and fitted parametric distributions for NIVO+IPI – weighted

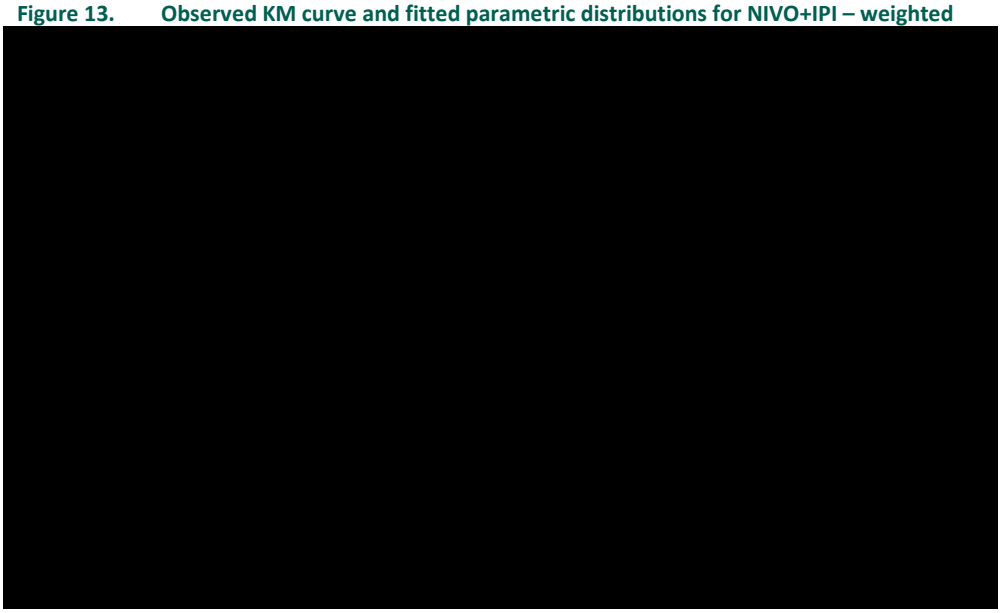


Figure 14. Observed KM curve and fitted parametric distributions for PEMBRO

On long-term extrapolations (see Section C.8.1.4.1), [redacted]

C.6.2.1 Extrapolated survival in weighted NIVO+IPI and PEMBRO

Based on the visual assessment of fit and statistical fits of the parametric survival models, [redacted] is the best-fitting distribution to model survival for NIVO+IPI and PEMBRO. The 5- and 10-year landmark survival predicted by the distributions are [redacted] respectively, for the NIVO+IPI arm and [redacted]

[redacted] for the PEMBRO arm. The predicted PFS for the NIVO+IPI arm is comparable to [redacted] NIVO+IPI in first-line mCRC patients in the CM 142 trial. [redacted]

The PFS KM curves for weighted NIVO+IPI and PEMBRO, as well as the long-term extrapolation based on the best-fitting [redacted] are shown in Figure 15. For comparison, the figure also presents the extrapolated survival of NIVO+IPI of the anchored ITC (as presented in Section C.4.2.1.3) analysis, [redacted]

Figure 15. PFS KM curves and extrapolated best-fitting distributions

The modelled hazards over time for NIVO+IPI and PEMBRO based on the best-fitting distribution can be found in Figure 16. [redacted]

Figure 16 PFS hazard curve of NIVO+IPI and PEMBRO based on the best-fitting distribution

C.6.2.2 Estimated time-varying HRs for NIVO+IPI vs. PEMBRO

The fitted parametric distributions were utilised to estimate hazards and their standard errors over time. Based on these, time-varying hazard ratios for each timepoint of the extrapolation were estimated along with their 95% CIs, as described in Section C.3.6.2. These estimated time-varying PFS HRs per trial are shown in Figure 17.

The point estimate of the time-varying HR

Figure 17. Time-varying PFS hazard ratio of NIVO+IPI vs. PEMBRO

Please note, that the green dotted line in the figure represents the estimated HR for NIVO+IPI vs. PEMBRO based on the Cox HR.

Table 20. Comparative analysis of studies comparing NIVO+IPI vs. PEMBRO for patients with mCRC

Outcome measure	Studies included in the analysis	Relative difference in effect HR (95% CI)		Method used for quantitative synthesis	Result used in the health economic analysis?
		Time (in months)	HR (95% CI)		
PFS	CM 8HW and KN-177	0	[redacted]	Unanchored matched adjusted indirect treatment comparison with time varying HRs	Yes
		12	[redacted]		
		24	[redacted]		
		36	[redacted]		
		48	[redacted]		
		60	[redacted]		
		72	[redacted]		
		84	[redacted]		

Outcome measure	Studies included in the analysis	Relative difference in effect HR (95% CI)		Method used for quantitative synthesis	Result used in the health economic analysis?
		Time (in months)	HR (95% CI)		
		96	[redacted]		
		108	[redacted]		
		120	[redacted]		

C.7 Discussion & conclusions

The phase 3 RCT, CM 8HW demonstrated a PFS benefit of NIVO+IPI vs. chemotherapy in the locally confirmed MSI-H/dMMR mCRC population. However, no head-to-head data is available to compare NIVO+IPI vs. its key comparator, PEMBRO, which was investigated in the KN-177 trial. To estimate the relative efficacy of NIVO+IPI vs. PEMBRO an ITC was conducted.

[redacted] matching the NIVO+IPI trial arm in CM 8HW to the PEMBRO trial arm in KN-177 in terms of TEMs and prognostic variables was chosen as the preferred analysis. Furthermore, [redacted]

[redacted] Scenario and sensitivity analyses conducted also provided comparable results.

However, this study is not without its limitations. [redacted] This analysis was also affected by data limitations, such

as the limited published summary statistics of KN-177. [redacted]

C.8 Appendix

C.8.1 Additional materials

C.8.1.1 Proportional hazards tests

The proportional hazards assumption (PHA) was tested for PFS via log-cumulative hazard plots, Schoenfeld residuals plots, and Grambsch and Therneau test to guide the choice of ITC methods regarding fixed or time-dependent treatment effect. The proportional-hazards assumption (PHA) testing for the KN-177 PFS data was performed using the pseudo-individual patient-level data generated from the published Kaplan-Meier (KM) curves and the IPD from CM 8HW.

[redacted]

Furthermore, also when comparing NIVO+IPI vs. PEMBRO [redacted]

Figure 18. Schoenfeld residual plots for PFS – KN-177

[redacted]

Figure 19. Log-cumulative hazards vs. log-time plots for PFS – KN-177

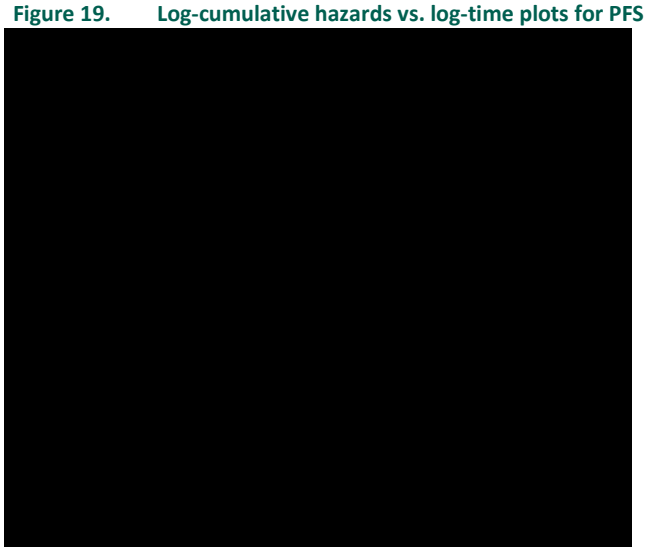


Figure 20. Schoenfeld residual plots for PFS – CM 8HW

Figure 21. Log-cumulative hazards vs. log-time plots for PFS – CM 8HW

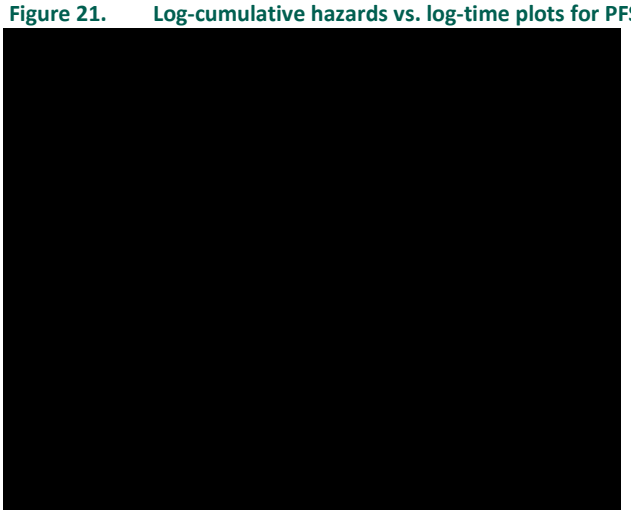


Figure 22. Schoenfeld residual plots for PFS – NIVO+IPI (unweighted) vs. PEMBRO

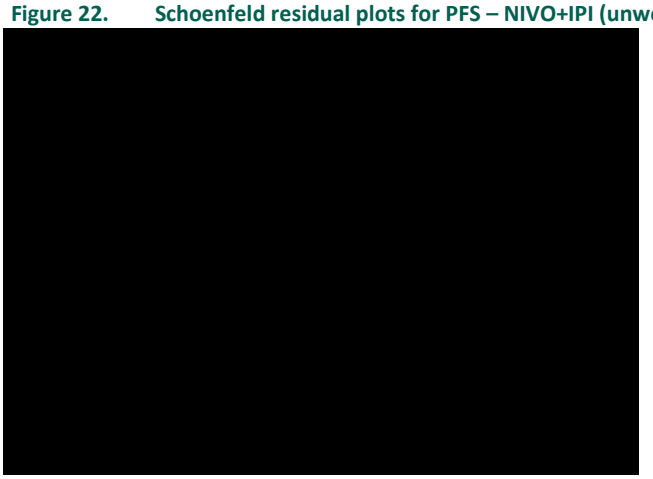


Figure 23. Log-cumulative hazards vs. log-time plots for PFS – NIVO+IPI (unweighted) vs. PEMBRO

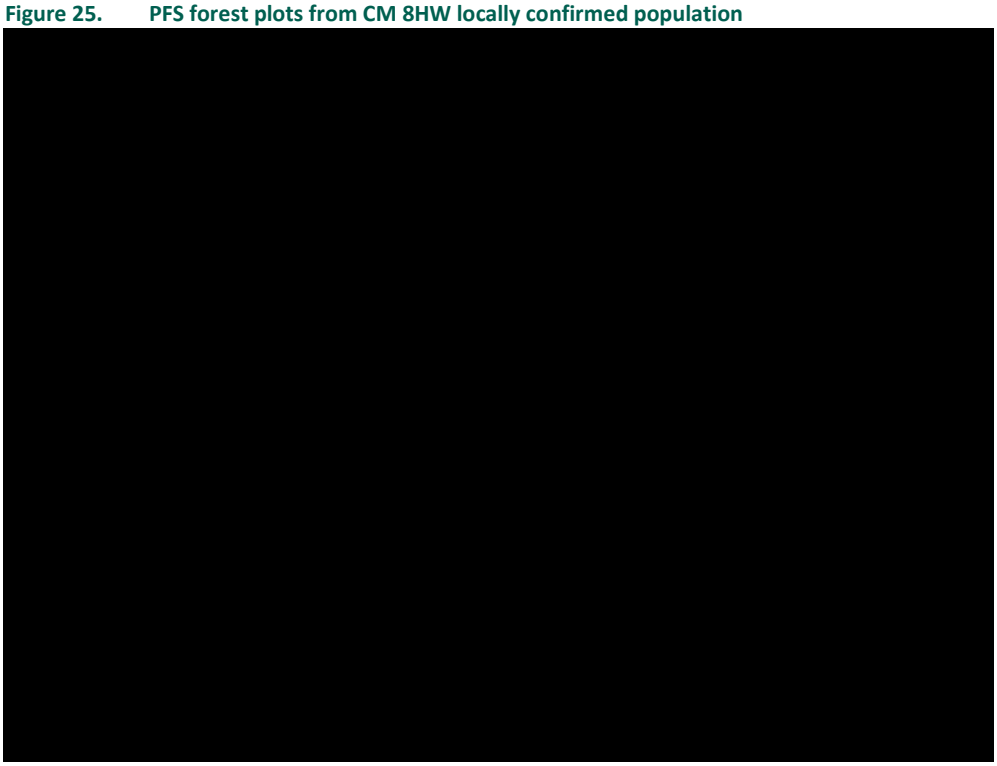
C.8.1.2 Subgroup forest plots informing treatment effect modifier selection

Figure 24. PFS forest plots from KN-177

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; KN = KEYNOTE; PFS = progression-free survival.

Source: Andre et al. (2020)[23]

Figure 25. PFS forest plots from CM 8HW locally confirmed population



Source: BMS data on file (2024)[24]

C.8.1.3 Matching variables – prognostic variables for the unanchored analysis

For the anchored analyses, [redacted]

[redacted]

Table 21. Recommended variables set (N = 14) of Goey et al. (2018)[25]

#	Variable in the recommended set of Goey et al.	Addition/Reason against addition
1	Age	[redacted]
2	ECOG performance status	[redacted]
3	Location (sidedness) of primary tumour	[redacted]
4	Surgery primary tumour	[redacted]
5	Prior chemotherapy	[redacted]
6	Number of metastatic sites	[redacted]
7	Liver-only disease	[redacted]
8	Liver involvement	[redacted]
9	Surgery metastases	[redacted]
10	Synchronous vs. metachronous metastases	[redacted]
11	KRAS mutation status	[redacted]
12	BRAF mutation status	[redacted]
13	MSI/MMR status	[redacted]

#	Variable in the recommended set of Goey et al.	Addition/Reason against addition
14	Number of prior treatment lines (for later-line trials)	[redacted]

C.8.1.4 Long-term survival extrapolations

C.8.1.4.1 CM 8HW matched to KN-177

Figure 26. Long-term PFS extrapolations of fitted parametric distributions for NIVO+IPI – weighted CM 8HW

[redacted]

Figure 27. Long-term PFS extrapolations of fitted parametric distributions for chemotherapy – weighted CM 8HW

[redacted]

C.8.1.4.2 KN-177

Figure 28. Long-term PFS extrapolations of fitted parametric distributions for PEMBRO – KN-177

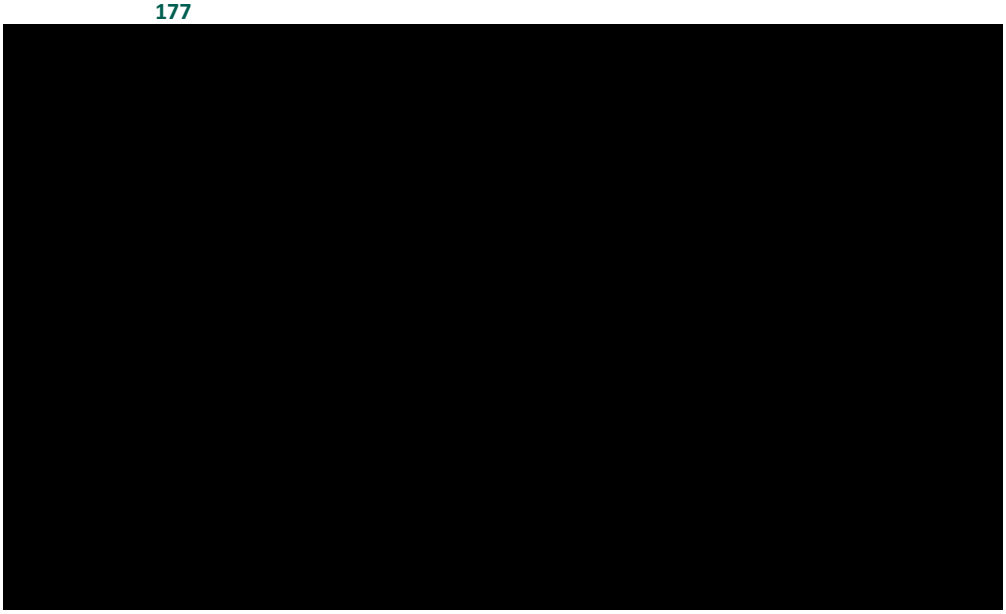


Figure 29. Long-term PFS extrapolations of fitted parametric distributions for chemotherapy – KN-177

C.8.1.4.3 NIVO+IPI of CM 8HW matched to PEMBRO of KN-177

Figure 30. Long-term PFS extrapolations of fitted parametric distributions for NIVO+IPI – weighted NIVO+IPI (unanchored analysis)

C.8.1.5 Time-varying hazard ratio: NIVO+IPI vs. PEMBRO, sensitivity analysis

The time-varying hazard ratios between NIVO+IPI vs. PEMBRO of the sensitivity analysis are shown in Figure 31.

Figure 31. Time-varying PFS hazard ratio of NIVO+IPI vs. PEMBRO, sensitivity analysis

C.8.2 Constant hazard ratio-based network meta-analysis (unweighted)

An HR-based NMA was performed as a scenario analysis. As the PHA was violated, the results from this method may be biased and should be interpreted with caution.

Table 22. Pairwise posterior estimates of hazard ratio and 95% credible intervals based on fixed effect Bayesian NMA

Treatment	Chemotherapy	NIVO+IPI	PEMBRO
Chemotherapy			
NIVO+IPI			
PEMBRO			

C.8.3 Smoothed hazard plots

Figure 32. Smoothed hazard plots of the standard parametric fits to CM 8HW chemotherapy arm weighted anchored MAIC analysis

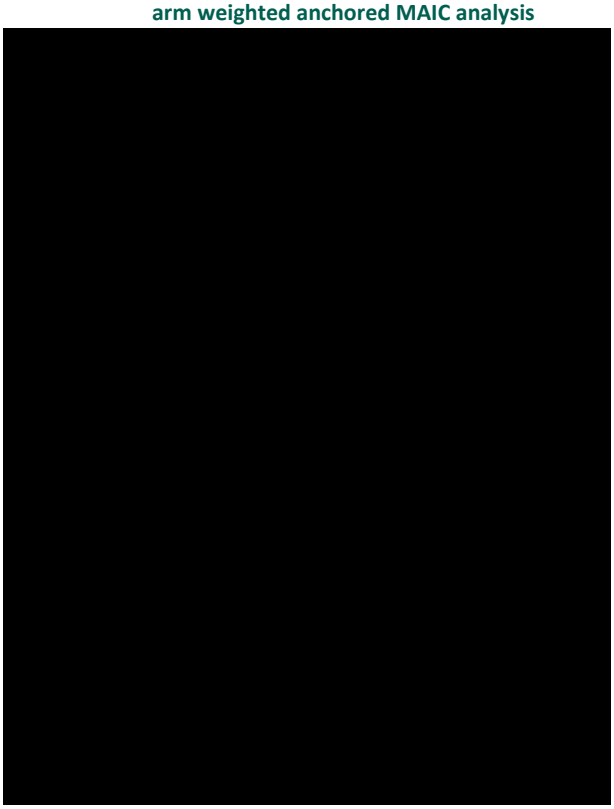


Figure 33. Smoothed hazard plots of the standard parametric fits to CM 8HW NIVO+IPI arm weighted anchored MAIC analysis

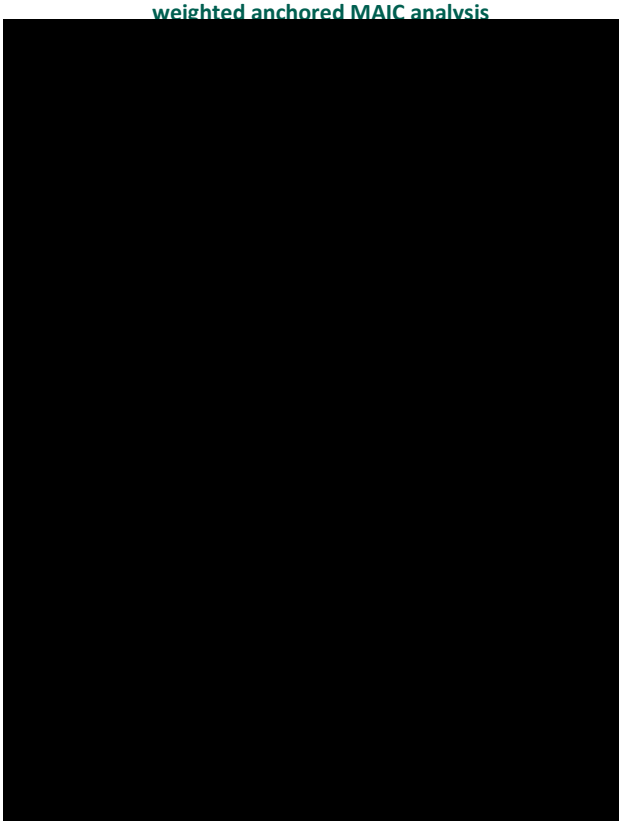


Figure 34. Smoothed hazard plots of the standard parametric fits to CM 8HW NIVO+IPI arm weighted unanchored MAIC analysis

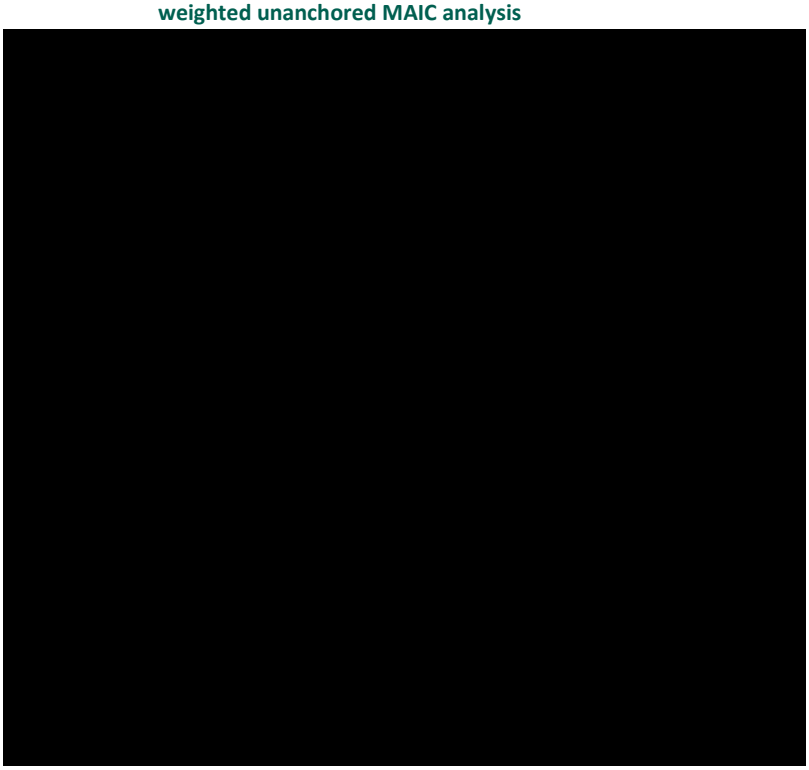


Figure 35. Smoothed hazard plots of the standard parametric fits to KN-177 chemotherapy arm

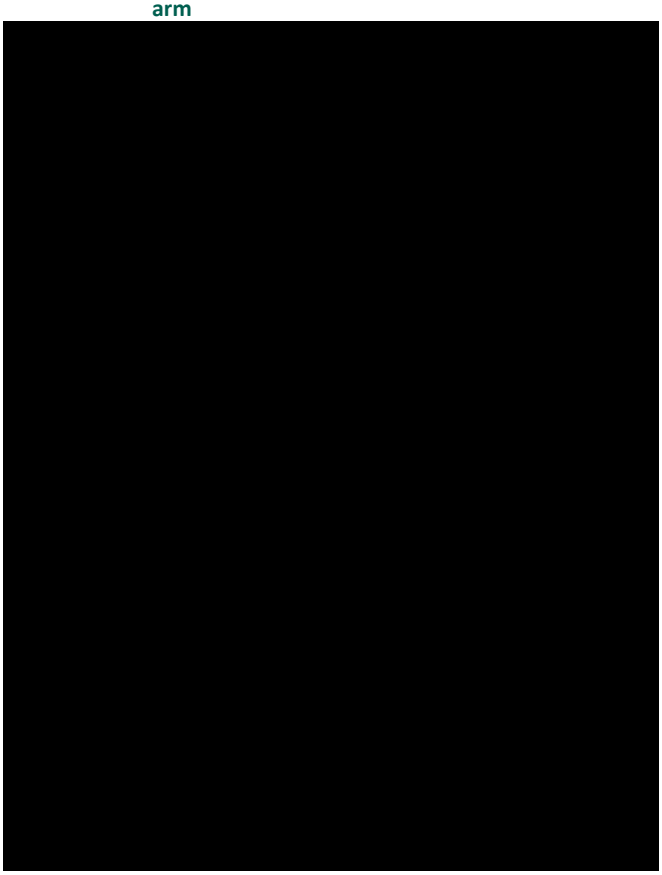
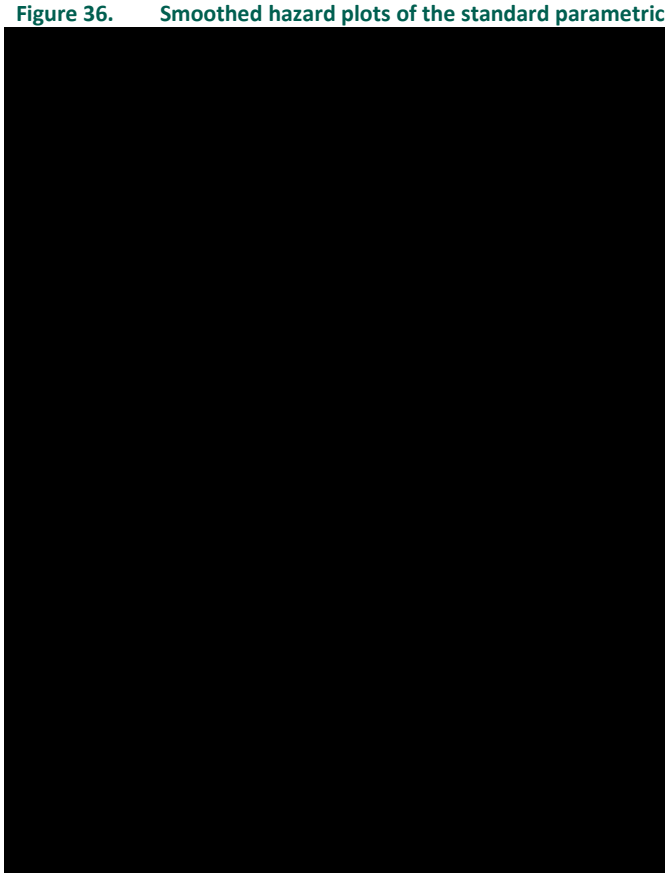


Figure 36. Smoothed hazard plots of the standard parametric fits to KN-177 PEMBRO arm



Appendix D. Extrapolation

D.1 Data input

The main data sources used to inform the CEM consist of time-to-progression (TTP) data from the December 2023 database lock (DBL) of the CM 8HW (NCT04008030) trial, as well as pre-progression and postprogression survival data from the October 2022 DBL of the CM 142 trial (NCT02060188).

D.1.1 CM 8HW trial

The CM 8HW trial is an ongoing phase III, randomised, parallel assignment trial that compares the impact of NIVO+IPI on the survival of 1L MSI-H/dMMR mCRC patients against an investigator's choice of chemotherapy. Participants receiving chemotherapy in CM 8HW were permitted to cross over to the NIVO+IPI treatment arm if they experienced documented progression of disease per RECIST 1.1 by BICR, provided that they completed at least one follow-up visit within the follow-up phase and met all other crossover criteria.

D.1.2 CM 142 trial

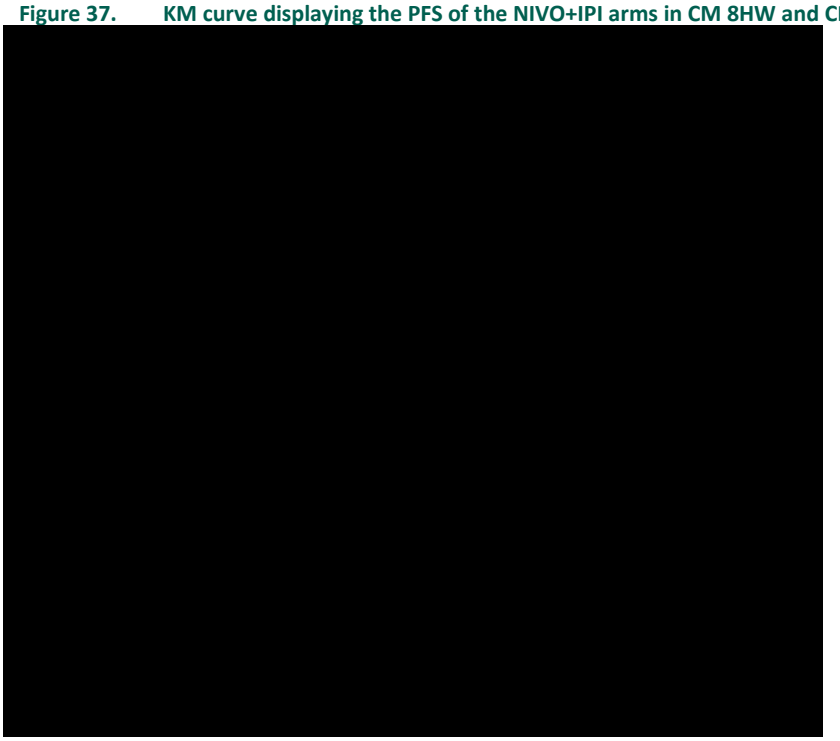
The CM 142 trial is a phase II, multicohort, non-randomised study of NIVO-based therapies in previously treated and untreated MSI-H and non-MSI-H mCRC patients. As OS data for CM 8HW is unavailable at the time of analysis, OS data from the NIVO+IPI arm of CM 142 (cohort 2 and 3) is used to inform the transition from PF to death ($p_{1,3}$, as scenario analysis) and the transition from PD to death ($p_{2,3}$).

D.1.2.1 Justification for the use of CM 142 data

As mentioned above, OS data from CM 142 has been used to estimate the transition from PD to death ($p_{2,3}$) as OS data from CM 8HW is unavailable. It is assumed that patients receiving NIVO+IPI in CM 142 are comparable to those in CM 8HW as they receive similar treatment assignments. Due to the similarities in both patient populations, an exploratory matching analysis was conducted to determine whether CM 142 data could be matched to CM 8HW and used to estimate the transition from PD to death ($p_{2,3}$).

Crucially, the main difference between both populations is that patients who receive NIVO+IPI in CM 142 comprise of 1L and 2L+ NIVO+IPI patients, whereas patients in CM 8HW receive NIVO+IPI as a 1L 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 CM 142 and 8HW, as well as the PF-to-PD transition ($p_{1,2}$), are similar (Figure 37, Figure 38). Thus, this supports our use of CM 142 OS data in the estimation of the transition from PF to death ($p_{1,3}$) and the transition from PD to death ($p_{2,3}$).

Figure 37. KM curve displaying the PFS of the NIVO+IPI arms in CM 8HW and CM 142



CM = CheckMate; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; PFS = progression-free survival.

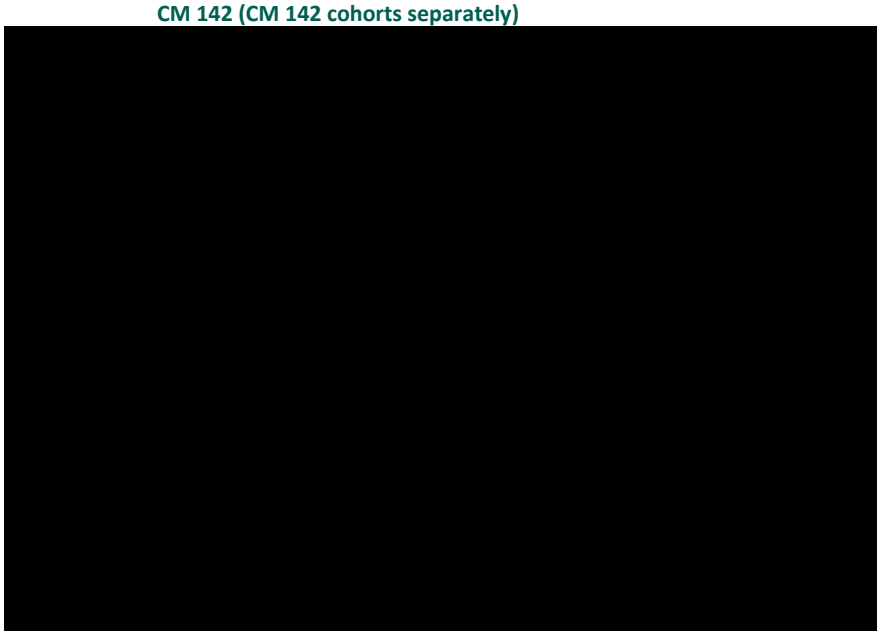
Figure 38. KM curve displaying the PFS of the NIVO+IPI arms in CM 8HW and CM 142 (CM 142 cohorts separately)

CM = CheckMate; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; PFS = progression-free survival.

Figure 39. KM curves of the PF-to-PD transition ($p_{1,2}$) for the NIVO+IPI arms in CM 8HW and CM 142

CM = CheckMate; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; PD = Progressed Disease; PF = Progression Free.

Figure 40. KM curves of the PF-to-PD transition ($p_{1,2}$) for the NIVO+IPI arms in CM 8HW and CM 142 (CM 142 cohorts separately)



CM = CheckMate; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; PD = Progressed Disease; PF = Progression Free.

D.2 Methods

A brief overview of the statistical methods used in this analysis are outlined below.

D.2.1 Exploratory matching analysis for postprogression survival

Prior to fitting standard parametric survival distributions to each transition, an exploratory matching analysis was conducted to determine whether matched and reweighted CM 142 data could be used to estimate the transition from PD to death ($p_{2,3}$) in lieu of CM 8HW data.

In the matching analysis, the ITT population from CM 142 was matched to the ITT population from CM 8HW, which resulted in the NIVO+IPI arm in CM 142 being matched to the chemotherapy and NIVO+IPI arms from CM 8HW. The matching analysis is carried out in this manner as it is assumed that postprogression survival between the chemotherapy and NIVO+IPI arms are equal. Furthermore, as mentioned in Section D.1.2, the ITT population in CM 142 comprises of 1L and 2L+ patients, which was matched to the 1L ITT population in CM 8HW.

The CM 142 population was matched to CM 8HW patients in a three-part process as outlined below.

D.2.1.1 Selection of matching variables

A multivariable Cox model is a survival analysis regression model where the hazard function of a certain timepoint is dependent on a set of covariates, *p*, whose impact is affected by the value of their respective coefficients *b* [26]. This is expressed in Equation 1 below:

$$h(t) = h_0(t) * \exp\left(b_1 x_1 + b_2 x_2 + \cdots b_p x_p\right)$$

Equation 1

The Cox model was used to determine the association between the PD-to-death ($p_{2,3}$) transition and covariates present in the CM 142 data. Variables considered for matching included important and suggested prognostic factors for mCRC patients identified in Goey et al. (2018)[25] such as MSI/dMMR status, prior chemotherapy, and K(RAS) mutation status. Variables were chosen through a backward stepwise selection, where predictors with weak or uncertain associations were removed. However, variables that were suggested to be important prognostic factors for mCRC patients by clinicians or experts were implemented as fixed components in the model, even if they were not selected in the backwards stepwise selection. The best-performing models were selected based on AIC,[27] with the model with the lowest AIC having the best relative model fit.

D.2.1.2 Reweighting CM 142 data using propensity score weighting

To adjust unbalanced covariates, a propensity score (PS) method was used to generate weights for CM 142 patients based on the identified variables. The PS score is the probability of assignment to a particular treatment conditional on certain characteristics (selected variables) or data source (CM 142 vs. CM 8HW). PS weighting was carried out using a logistic regression in which the dependent variable was a dummy variable indicating treatment participation, and this can be defined mathematically in Equation 2 below:

$$logit(Probability\ of\ treatment\ participation) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + . \beta_n x_n$$

Equation 2

Where β is the estimated coefficient associated with *n* selected study covariates.

Once the PS was calculated, the nearest-neighbour matching algorithm was applied without replacement and a caliper width of 0.2 was applied to ensure that all variables were balanced and had a standardised mean difference (SMD) < 0.1.[28] Matching with replacement was allowed to compensate for the difference in sample sizes between the CM 142 and CM 8HW populations. After this, the PS were used as weights and applied to the CM 142 population to generate a population that was more similar to CM 8HW. Estimates of the ESS, which is a measure of the reduction in size of the control group based on PS weights,[29] were also obtained.

D.2.1.3 Validation of the CM 142 matching and reweighting workstream

To verify that CM 142 data was successfully matched to CM 8HW data, the shape of the PF-to-PD ($p_{1,2}$) curve of CM 8HW was compared against the PF to PD ($p_{1,2}$) of the weighted CM 142 patients to ensure that the matching process generated the same outcomes for both transitions.

D.2.2 Proportional hazard (PH) assumption

The validity of the PH assumption was assessed for the PF-to-PD transition ($p_{1,2}$) to inform the choice between dependent and independent parametric models. For independent models, an individual parametric model is fitted for each stratum (i.e., treatment received). With dependent models a single parametric model is fitted to both strata, featuring an indicator variable for the strata as a covariate. As they do not assume any relationship between the strata, independent models require fewer assumptions, but more parameter estimations are required compared with dependent models. If the PH assumption is rejected, independent models are preferred. If it is not rejected, a HRs can be used to express the difference in hazards between strata and a dependent model approach can be used.

The PH assumption between NIVO+IPI and chemotherapy were assessed for the ITT population and centrally confirmed group for the PF-to-PD transition ($p_{1,2}$). Similarly, the PH assumption between NIVO+IPI and PEMBRO were assessed in the ITC workstream (see Section 7 of the main submission). As postprogression survival and the PF-to-Death transition ($p_{1,3}$) is assumed to be equal for all treatment arms, testing for the validity of the PH assumption was not required for these transitions.

To determine whether the PH assumption is held, the time dependency of the HRs is tested, which is equivalent to testing for a non-zero slope in a generalised linear regression of scaled Schoenfeld residuals over time. 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 is zero. If the *P* value produced from the chi-square test is significant (< 0.05), the null hypothesis of the PH is rejected.

D.2.3 Standard parametric survival distributions

Standard parametric models (exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, Weibull) were fitted to each transition to obtain estimates of TPs that were beyond the trial period.

As standard parametric models do not account for the impact of background mortality, extrapolated results which estimate survival rates superior to those of the general population may be produced, which is unviable. The parametric models were adjusted for background mortality within the CEM where the rate of progression to the death health state due to natural causes was incorporated in the derivation of any PF-to-PD ($p_{1,2}$) transitions. This was conducted using the Danish life tables.[30] The best model fit at each transition will be based on the model selection algorithm outlined in Palmer et al. (2023)[31], 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 both UK and global advisory board meetings to ensure that the TPs derived were clinically plausible. Survival estimates from R will also be validated against Excel-derived outputs from the CEM.

D.3 Extrapolation of transitions from progression-free to progressed disease

Although chemotherapy is not included as a comparator in the economic analysis, the survival analysis for chemotherapy is presented in this section to provide a comprehensive insight of the extrapolation of survival outcome.

D.3.1 NIVO+IPI vs. chemotherapy

For NIVO+IPI and chemotherapy, the transition from PF to PD ($p_{1,2}$) was estimated by fitting parametric models to the TTP data from CM 8HW. There was a total of 303 patients included in this transition, 202 of which receive NIVO+IPI and 101 of which received chemotherapy.

Among NIVO+IPI patients, the median TTP (in month, Figure 39) was not reached (95% CI, 38.44 to not reached), while among chemotherapy patients the median TTP was 7.39 months (95% CI, 5.68-10.90). In the NIVO+IPI arm, the 1-year progression-free probability was 0.75 (95% CI, 0.69-0.82), while in the chemotherapy arm it was 0.32 (95% CI, 0.22-0.47). The calculated HRs between the two trial arms, under the proportional hazards (PH) assumption, was 0.34 (95% CI, 0.223-0.51).

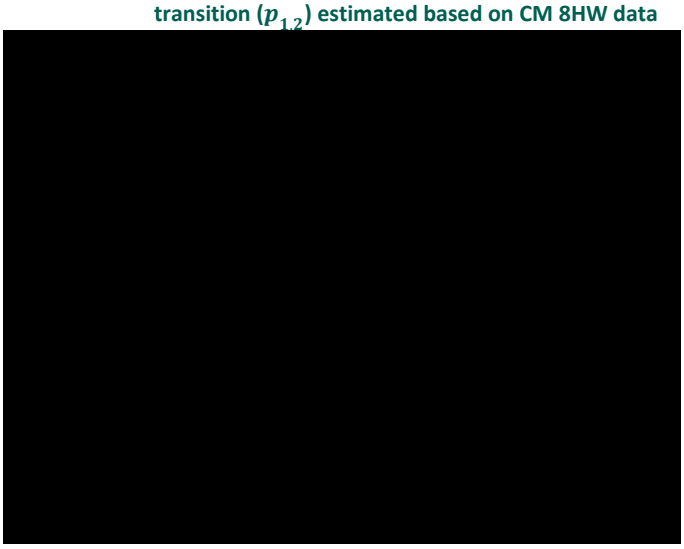
Figure 41. KM curve presenting the PF-PD transition ($p_{1,2}$) for the NIVO+IPI and chemotherapy arms in CM 8HW

CM = CheckMate; IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab.

D.3.1.1 Proportional hazard (PH) tests

The scaled Schoenfeld residuals plot is shown in Figure 40 for the PF-to-PD transition ($p_{1,2}$). The *P* value obtained on the non-zero slope test was < 0.001, indicating that hazards do not remain constant over time.

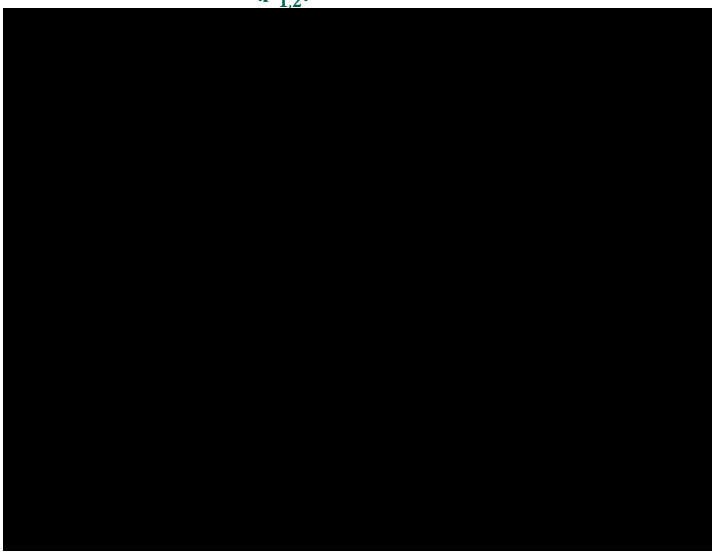
Figure 42. Scaled Schoenfeld residuals plot for NIVO+IPI vs. chemotherapy for the PF-to-PD transition ($p_{1,2}$) estimated based on CM 8HW data



CM = CheckMate; IPI = ipilimumab; NIVO = nivolumab; PD = Progressed Disease; PF = Progression Free.

The log-cumulative hazard plot against log-time is also shown in Figure 41. For patients receiving NIVO+IPI vs. chemotherapy, the log-cumulative hazards are not parallel, and they cross several times. Therefore, the PH assumption is rejected, and as a result only independent curves were fitted.

Figure 43. Log-cumulative hazards plot for NIVO+IPI vs. chemotherapy for the PF-to-PD transition ($p_{1,2}$) estimated based on CM 8HW data



CM = CheckMate; IPI = ipilimumab; NIVO = nivolumab; PD = Progressed Disease; PF = Progression Free.

D.3.1.2 Evaluation of statistical fit

As the PH assumption did not hold, independent models were fit to the data. Standard parametric models were fit to both the NIVO+IPI and chemotherapy arms from CM 8HW independently to estimate the TP for PF to PD ($p_{1,2}$). Model fits were then extrapolated beyond the observed period of the CM 8HW to derive an estimate of the long-term TP of PF to PD ($p_{1,2}$) for each treatment arm. The AIC values for all fits to the NIVO+IPI and chemotherapy data can be found in Table 23.

Table 23. AIC values for standard parametric fits for the PF-to-PD transition ($p_{1,2}$) fit to CM 8HW NIVO+IPI and chemotherapy data

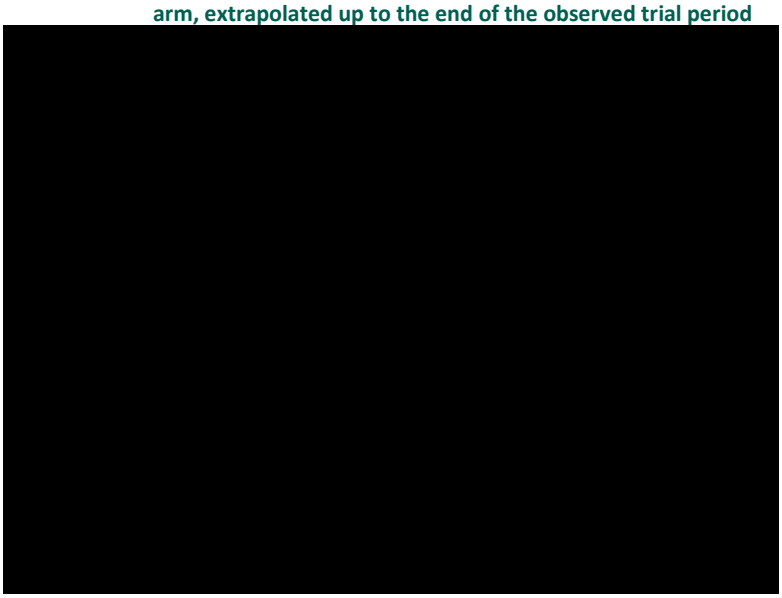
PF-to-PD Transition ($p_{1,2}$)	CM 8HW			
	NIVO+IPI AIC	NIVO+IPI BIC	Chemotherapy AIC	Chemotherapy BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

AIC = Akaike information criteria; CM = CheckMate; IPI = ipilimumab; NIVO = nivolumab; PD = Progressed Disease; PF = Progression Free.

D.3.1.3 Evaluation of visual fit

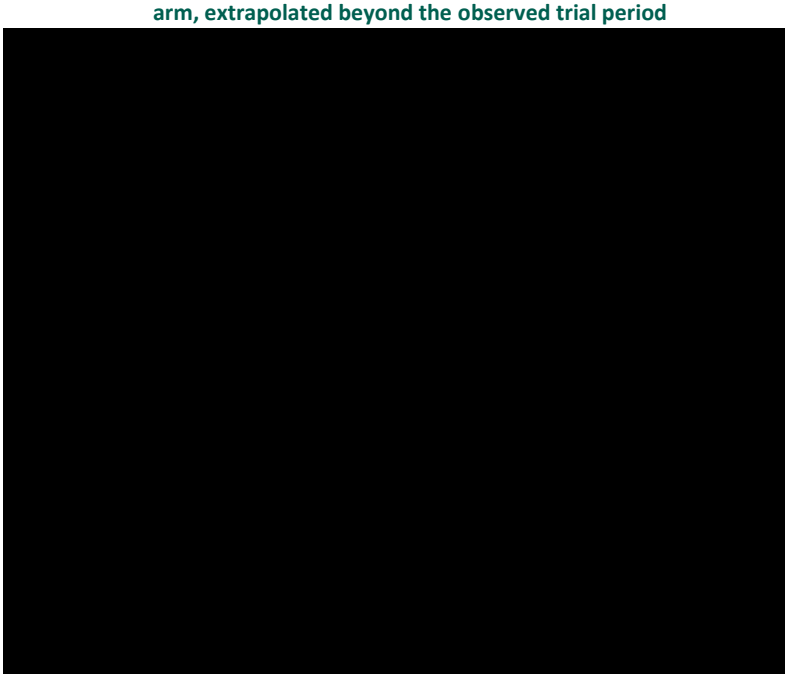
Extrapolated curves for NIVO+IPI are presented in Figure 42 and Figure 43, respectively. Extrapolated curves for chemotherapy are presented in Figure 44 and Figure 45, respectively.

Figure 44. Standard parametric fits of the PF-PD transition ($p_{1,2}$) for the CM 8HW NIVO+IPI arm, extrapolated up to the end of the observed trial period



CM = CheckMate; IPI = ipilimumab; NIVO = nivolumab; PD = Progressed Disease; PF = Progression Free.

Figure 45. Standard parametric fits of the PF-PD transition ($p_{1,2}$) for the CM 8HW NIVO+IPI arm, extrapolated beyond the observed trial period



CM = CheckMate; IPI = ipilimumab; NIVO = nivolumab; PD = Progressed Disease; PF = Progression Free.

Figure 46. Standard parametric fits of the PF-PD transition ($p_{1,2}$) for the CM 8HW chemotherapy arm, extrapolated up to the end of the observed trial period

CM = CheckMate; PD = Progressed Disease; PF = Progression Free.

Figure 47. Standard parametric fits of the PF-PD transition ($p_{1,2}$) for the CM 8HW chemotherapy arm, extrapolated beyond the observed trial period

CM = CheckMate; PD = Progressed Disease; PF = Progression Free.

D.3.1.4 Evaluation of hazard function

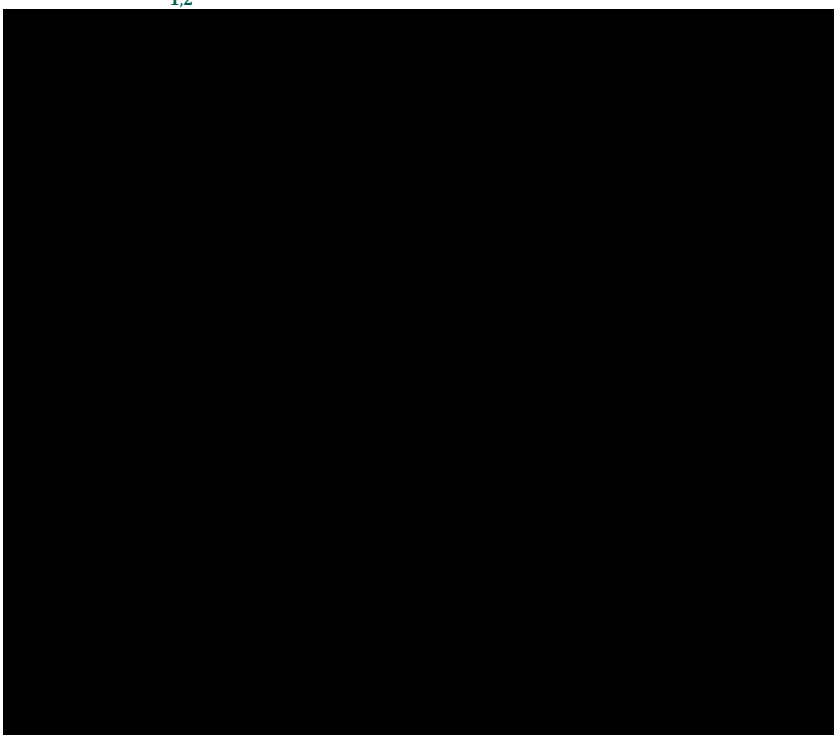
Landmark survival values for NIVO+IPI and chemotherapy can be found in Table 24. The corresponding smoothed hazard plots of the extrapolated curves for NIVO+IPI and chemotherapy can be found in Figure 46 and Figure 47, respectively.

Table 24. Landmark survival estimates (years) of the standard parametric fits of the PF-to-PD transition ($p_{1,2}$) for the CM 8HW NIVO+IPI and chemotherapy arms

	NIVO+IPI					Chemotherapy				
	Median TTP	1 year	5 years	10 years	20 years	Median TTP	1 year	5 years	10 years	20 years
Observed	[redacted]									
Exponential	[redacted]									
Gamma	[redacted]									
Generalised gamma	[redacted]									
Gompertz	[redacted]									
Log-logistic	[redacted]									
Log-normal	[redacted]									
Weibull	[redacted]									

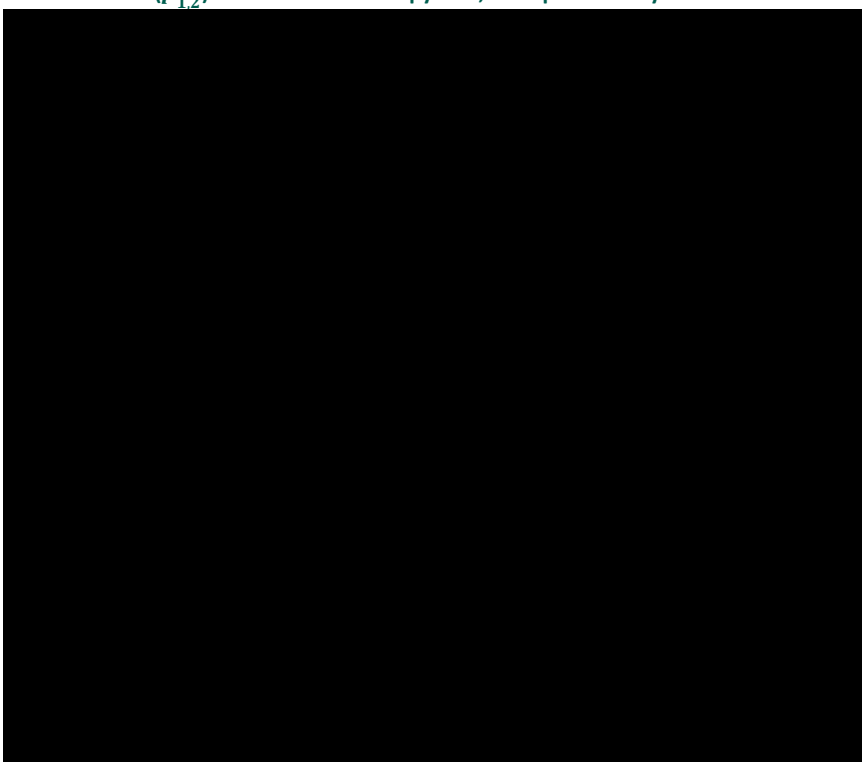
CM = CheckMate; IPI = ipilimumab; NIVO = nivolumab; NR = not reached; PD = Progressed Disease; PF = Progression Free; TTP = time to progression.

Figure 48. Smoothed hazard plots of the standard parametric fits to the PF-to-PD transition ($p_{1,2}$) for the NIVO+IPI arm, extrapolated beyond the observed trial period



IPI = ipilimumab; NIVO = nivolumab; PD = Progressed Disease; PF = Progression Free.

Figure 49. Smoothed hazard plots of the standard parametric fits to the PF-to-PD transition ($p_{1,2}$) for the chemotherapy arm, extrapolated beyond the observed trial period



PD = Progressed Disease; PF = Progression Free.

D.3.1.5 Summary and discussion

For the NIVO+IPI arm, of the seven parametric models fit the exponential and Gompertz can be excluded immediately based on unrealistic extrapolations as seen in Figure 43, with the exponential predicting a steep decline in progression-free probability and the Gompertz predicting an unrealistically high long-term progression-free probability. Of the five remaining candidate fits, the generalised gamma, log-normal, and log-logistic fits had the lowest AIC values. Looking at the extrapolations in Figure 43, the generalised gamma fit provides a more optimistic extrapolation than both log-logistic and log-normal, which behave comparably to one another. This is further supported by the landmark survival estimates found in Table 24, with the generalised gamma fit having a median TTP of 21.3 years (95% CI, 4.6, NR) while log-logistic had a median TTP of 5.4 years (95% CI, 3.0, 9.4) and log-normal 5.7 years (95% CI, 3.1, 10.7). Further, the generalised gamma provides the closest fit to the data in the first 6 months, as the only curve to capture the "hockey stick" shape of the observed data. The "hockey stick" shape that was observed for the TTP data of NIVO+IPI is due to a higher number of events being observed at the start of the trial as opposed to the rest of the trial duration. This may be because patients may have progressed before the treatment they received had a chance to start displaying its efficacy. Survival curves with this shape are difficult for some parametric distributions to fit, particularly those with too few parameters to adjust to the curve shape.

The generalised gamma model was chosen to extrapolate TTP for NIVO+IPI for a number of reasons:

- Its fit to the observed data based on AIC: The AIC value for the generalised gamma model is significantly lower (989.4 vs. 1,012.8 for log-normal and 1,019.8 for log-logistic). The smoothed hazard plots also support this, as the generalised gamma fit provides the closest fit to the hazards estimated in the NIVO+IPI arm.
- Performance relative to other parametric curves: Most extrapolations (Weibull, log-logistic, gamma, exponential) fail to capture the initial increase in hazards in the NIVO+IPI arm.
- Consistency with the types of models chosen for other portions of the model for TTP, including models fit to data after the MAIC: These choices were also in line with what was recommended in NICE DSU TSD 14, [32] which recommends fitting the same type of model for each treatment arm when parametric models are fitted separately to individual treatment arms.

Therefore, utilisation of the generalised gamma model for NIVO+IPI is in line with best practice, particularly as parametric alternatives considered (log-normal and log-logistic) did not perform significantly better in terms of fit statistics or adherence to the shape of the observed data. Furthermore, the generalised gamma model was validated against the best-fitting standard parametric fit to CM 142 NIVO monotherapy data through 5 years, and its values were found to be clinically plausible.

For the chemotherapy arm, all models show similar shapes within the observed time window of 1.25 years, shown in Figure 44. 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 45, 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 23) in order were log-normal (687.2), generalised gamma (687.4), and log-logistic (688.1). Comparing the landmark survival values of these three fits in Table 24 shows that generalised gamma and log-logistic both precisely match the observed median TTP of 7.4 months, while the log-normal point estimate is slightly higher at 8.3 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 log-normal and log-logistic models is identical, with estimates slightly lower than the generalised gamma.

Regarding the smoothed hazard plots shown in Figure 47, the generalised gamma, log-normal, and log-logistic extrapolations are the most realistic, as they all capture the initial increase in hazards exhibited by the chemotherapy arm, but then predict a decrease in hazards over time which is what is expected as patients start to respond to treatment. The smoothed hazards predicted by the Gompertz distribution is pessimistic, whereas Weibull and Gamma predict an increase or a plateau in hazards, respectively, which may not be realistic.

Thus, given the comparable performance of the log-normal and generalised gamma fits, and that generalised gamma was recommended for CM 8HW NIVO+IPI arm, it is also recommended here for chemotherapy for consistency.

D.3.2 Extrapolation for NIVO and IPI vs. PEMBRO

As outlined in Section 8.2 in the main submission, due to no direct evidence available comparing PEMBRO with NIVO+IPI in MSI-H mCRC patients, a MAIC was performed using aggregate data from KN-177 and IPD from CM 8HW.

D.4 Extrapolation for transitions from progression-free to death ($p_{1,3}$)

As outlined in Section 8.3 in the main submission, there are two data sources that can be used to estimate the transition from PF to death ($p_{1,3}$): CM 142 PF-to-Death ($p_{1,3}$) data, and background mortality data. While the background mortality data was modelled as the base case scenario, the functionality to use CM 142 data in the transition from PF to death ($p_{1,3}$) has been included in the model should users wish to use CM 142 data for PF to death ($p_{1,3}$) instead. Details on the PF-to-Death transition derived from the CM 142 data are presented below.

D.4.1 Extrapolation based on CM 142 data

There was a total of 164 patients included in this transition, all of which received NIVO+IPI. The median time to death (in months) was not reached (95% CI NR – NR), and the 1-year death-free probability was 0.93 (95% CI, 0.89-0.98).

D.4.1.1 PH tests

The PH assumption was not evaluated as only the NIVO+IPI arm in CM 142 (comprising of cohorts 2 and 3) was used to estimate the transition from PF to death ($p_{1,3}$).

D.4.1.2 Evaluation of statistical fit

Standard parametric models were fit to the CM 142 independently to estimate the transition probability for PF to death ($p_{1,3}$). The AIC values for these fits can be found in Table 25.

Table 25. AIC values for standard parametric fits for the PF-to-Death ($p_{1,3}$) transition fit to CM 142 data

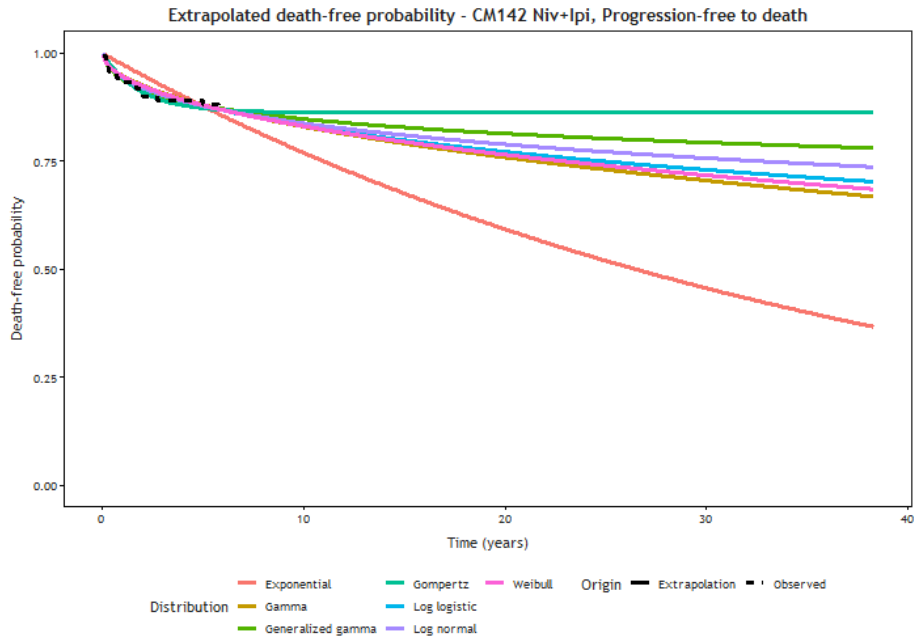
PF-to-Death Transition ($p_{1,3}$)	CM 142 AIC	CM 142 BIC
Exponential	339.4	342.5
Gamma	331.7	337.9
Generalised gamma	331.7	341.0
Gompertz	331.6	337.8
Log-logistic	331.3	337.5
Log-normal	330.3	336.5
Weibull	331.5	337.7

AIC = Akaike information criteria; BIC = Bayesian information criteria; CM = CheckMate; PF = Progression Free.

D.4.1.3 Evaluation of visual fit

Extrapolated curves are presented in Figure 48.

Figure 50. Standard parametric fits of the PF-to-Death transition ($p_{1,3}$) for CM 142, extrapolated beyond the observed trial period



CM = CheckMate; PD = Progressed Disease; PF = Progression Free.

D.4.1.4 Evaluation of hazard function

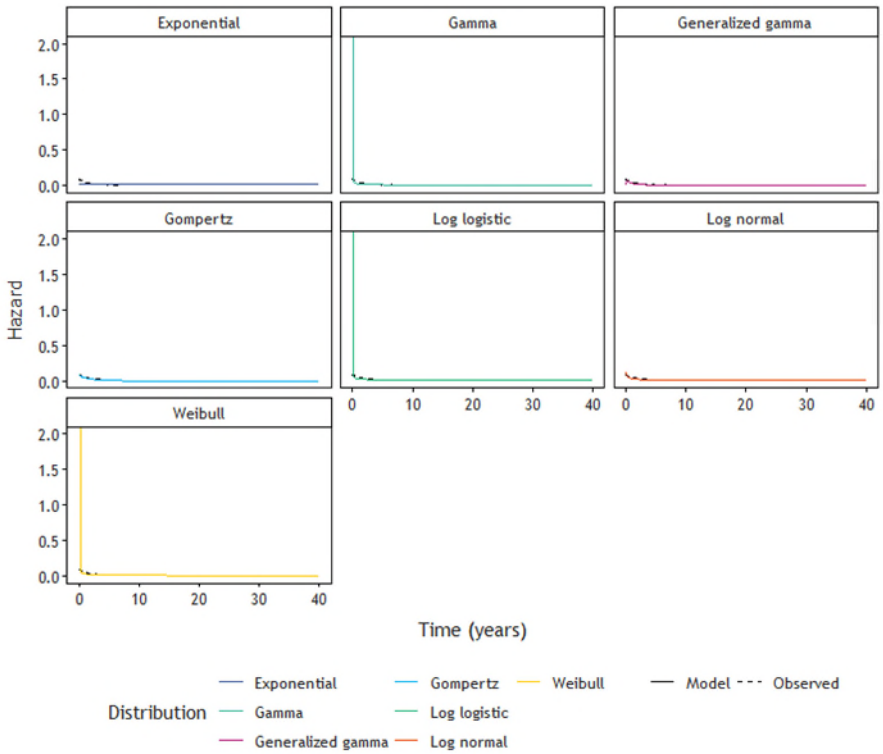
The landmark survival values can be found in Table 26. The corresponding smoothed hazard plots for these extrapolations can be found in Figure 49.

Table 26. Landmark survival estimates (years) of the standard parametric fits of the PF-to-Death transition ($p_{1,3}$) for the CM 142 data

	Median TTP	1 year	5 years	10 years	20 years
Observed	NR	0.93	0.88	NR	NR
Exponential	26.5	0.97	0.88	0.77	0.59
Gamma	NR	0.95	0.88	0.83	0.76
Generalised gamma	NR	0.94	0.88	0.85	0.81
Gompertz	NR	0.94	0.87	0.86	0.86
Log-logistic	NR	0.95	0.88	0.83	0.77
Log-normal	NR	0.94	0.88	0.84	0.79
Weibull	NR	0.95	0.88	0.83	0.77

CM = CheckMate; PF = Progression Free; TTP = time to progression; NR = not reached.

Figure 51. Smoothed hazard plots of the standard parametric fits to the PF-to-Death transition ($p_{1,3}$) for CM 142, extrapolated beyond the observed trial period



CM = CheckMate; PF = Progression Free.

D.4.1.5 Summary and discussion

Of the models fit, all provide unrealistic extrapolations for the outcome of death without progression within this population, with the least optimistic predicting a 59% death-free probability at 20 years (exponential) and most optimistic predicting an 86% death-free probability (Gompertz). In terms of AIC, most models had similar values, but the log-normal was the overall lowest at 330.3 as shown in Table 25.

This model also had an overestimating similar set of landmark survival values to other models as shown in Table 26, and fell somewhat in the middle in the long-term extrapolation plots in Figure 48. Similarly, in the smoothed hazard plots shown in Figure 49, only the log-normal, generalised gamma, and Gompertz distribution seemed to have a good fit to the observed hazards, with the Weibull, log-logistic, and gamma distributions overestimating the increase in hazards observed at the start of the trial. Therefore, the log-normal model was selected for use in the sensitivity analysis where the max of the transition probability estimated by this model or background mortality is used.

D.5 Extrapolation for transitions from progressed disease to death

As CM 8HW OS data was unavailable, CM 142 data was used in lieu of CM 8HW data for estimating the transition from PD to death ($p_{2,3}$). As mentioned in Section 8.1 in the main submission, it is assumed that postprogression survival between all treatment arms (i.e., NIVO+IPI, PEMBRO) is equal. Therefore, only CM 142 data was used to estimate this transition. This was justified as CM 142 data was comparable to that of CM 8HW (see Section 8.1 in the main submission).

To make the CM 8HW and CM 142 populations more comparable, an exploratory matching analysis was carried out to determine if CM 142 data could be matched to CM 8HW to make the populations more similar. The analysis was carried out to also determine if this matched and reweighted CM 142 data could be used to estimate the PD-to-death transition ($p_{2,3}$) instead of using unmatched CM 142 data.

D.5.1 Results of exploratory matching analysis

D.5.1.1 Selection of matching variables

For the stepwise regression analysis, the covariates that were considered for matching included: age, sex, race, MSI-H status, lactate dehydrogenase levels, weight, prior smoking history, BRAF mutation status, KRAS mutation status, ECOG score, and disease stage at first diagnosis. These variables were chosen based on prognostic factors identified in Goey et al. (2018)[25]. The model that had the lowest AIC was one that composed of age, MSI-H status, and sex, as outlined in Table 27.

Table 27. AIC scores of models fit to covariates in the stepwise regression analysis

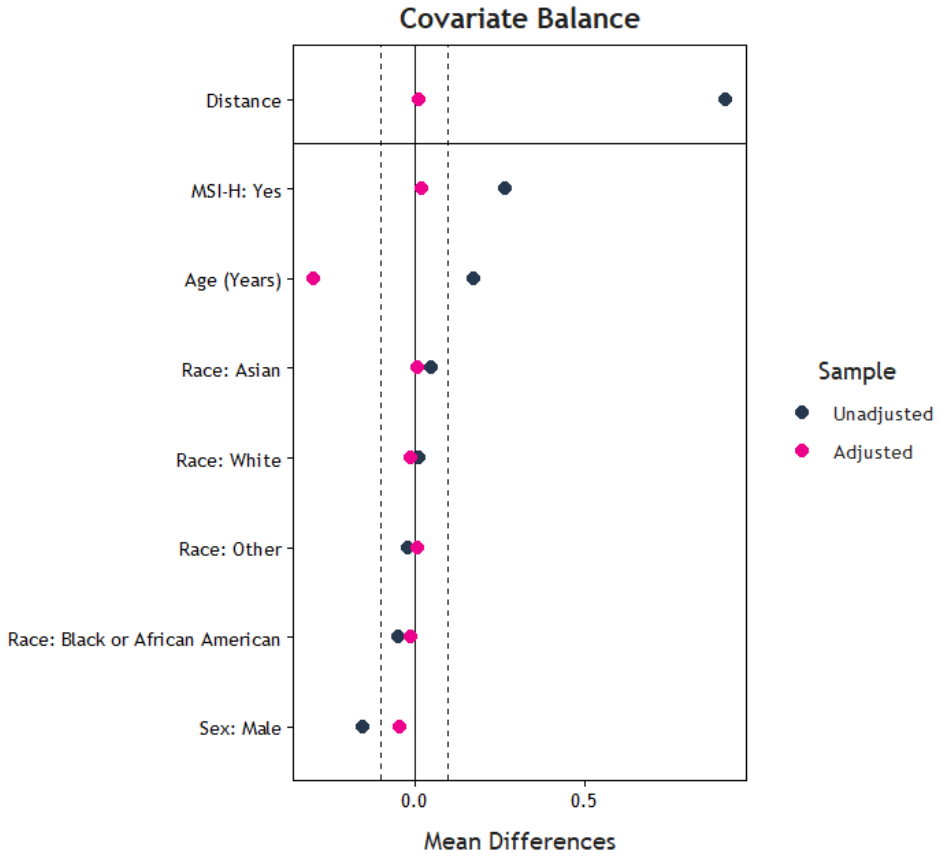
Model	AIC
Age, MSI-H status, sex	93.8
Adding prior smoking history	95.5
Adding race	97.0
Adding baseline lactate dehydrogenase levels	98.5
Adding ECOG score	100.3
Adding weight at baseline	102.2
Adding BRAF mutation status	105.9
Adding KRAS mutation status	110.4
Adding disease stage at first diagnosis	115.0

AIC = Akaike information criteria; ECOG = Eastern Cooperative Oncology Group; MSI-H = microsatellite instability-high.

However, the final model used in the matching analysis was one that contained the covariates age, race, and MSI-H status. The variable 'race' was selected to account for differences in the population between CM 8HW and CM 142, despite the exclusion of the variable from the most parsimonious model as determined by AIC, as race has been shown to be a factor that affects mCRC prognosis.[33]

In contrast, the variable 'sex' was excluded from the final model. This was conducted to improve the balancing between both trials, as the inclusion of sex led to the variable age being unbalanced in the model (Figure 50). When comparing the matching between a model that only included sex, race, and MSI-H status with a model that only included age, race, and MSI-H status, the ESS of the model including age instead of sex was higher (Table 28). Therefore, the covariates age, race, and MSI-H status were selected to fulfil both balanced variable and ESS requirements for matching.

Figure 52. Standardised Mean Differences of the adjusted and unadjusted CM 142 data, adjusting for Race, age, MSI-H status, and sex



CM = CheckMate; MSI-H = microsatellite instability-high.

Table 28. The ESS for the matched and reweighted CM 142 population compared with the ESS of the CM 8HW population for the two different models described above

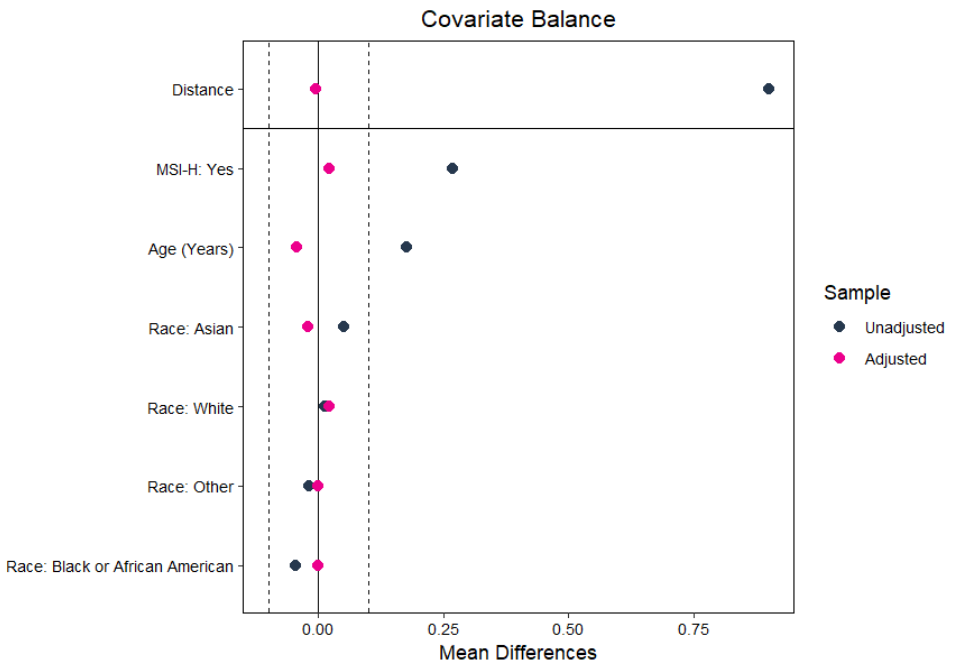
	ESS	
Model variables	**CM 142**	**CM 8HW**
Sex, race, MSI-H status	2.9	93
Age, race, MSI-H status	17.0	93

CM = CheckMate; ESS = effective sample size; MSI-H = microsatellite instability-high.

D.5.1.2 Reweighting CM 142 data using PS weighting

Matching the CM 142 population to the CM 8HW population resulted in balanced covariate distributions between both cohorts, where the SMD was < 0.1 as shown in Figure 51. However, the final matched CM 142 cohort was reduced to 43.8% (n = 25) of the original sample size (Table 29).

Figure 53. Standardised mean differences of the covariates used to match CM 142 to CM 8HW data



CM = CheckMate; MSI-H = microsatellite instability-high.

Table 29. Sample size of the matched and unmatched CM 142 and CM 8HW populations at postprogression

	Before matching		After matching	
Covariate	**CM 142**	**CM 8HW**	**CM 142**	**CM 8HW**
Population size	57	111	25	93
Age [mean], (SD)	61.8 (14.3)	60.12 (14.9)	59.4 (13.2)	61.6 (14.8)
MSI-H: Yes, n (%)	20 (55.6)	84 (82.4)	16 (64.0)	75 (80.6)
Race, n(%)				
American Indian or Alaska Native	1 (1.8)	0 (0.0)	-	-
Asian	1 (1.8)	9 (8.1)	1 (4.0)	1 (1.1)
Black or African American	3 (5.3)	1 (0.9)	-	
White	51 (89.5)	100 (90.1)	24 (96.0)	92 (98.9)
Other	1 (1.8)	1 (0.9)	-	

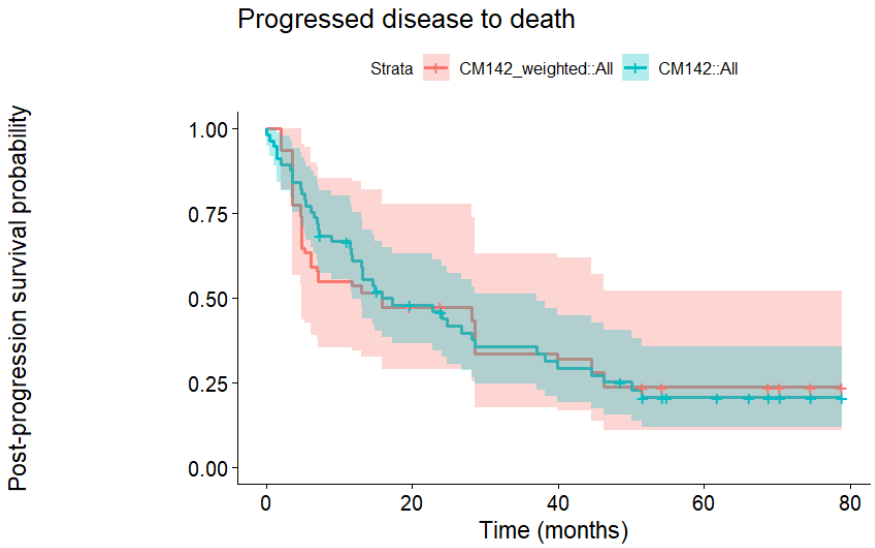
CM = CheckMate; MSI-H = microsatellite instability-high.

Additionally, the final matched population did not contain any patients whose race was classified as 'Black' or 'Other,' suggesting that these patients were discarded as a result of matching. However, the number of patients in these categories are low (Table 29); therefore, their exclusion is unlikely to have a large impact on the weights produced. Similarly, one patient who identified as 'American Indian or Alaskan Native' in CM 142 was excluded from the matching analysis as there were no patients who fit that category in CM 8HW.

D.5.1.3 Matching of CM 142

The matching analysis resulted in a small ESS due to weighting (ESS is n = 17 in the matched CM 142 data versus n = 164 in the unmatched CM 142 population), and it was found that the KM curves produced by the matched CM 142 data were comparable to the unmatched CM 142 data as the 95% confidence intervals of both overlapped. Moreover, the median survival of the matched CM 142 was equal to that of the unmatched one (15.9 months). However, there was more uncertainty associated with the estimates of transitions from PD to death as reflected in Figure 52. This is likely due to the large reduction in sample size caused by matching, which could be driven by differences in study design and patient characteristics.

Figure 54. KM curve of the matched and reweighted CM 142 PD-to-death transition ($p_{2,3}$) versus the unmatched CM 142 PD-to-death transition ($p_{2,3}$)



CM = CheckMate; KM = Kaplan-Meier; PD = Progressed Disease.

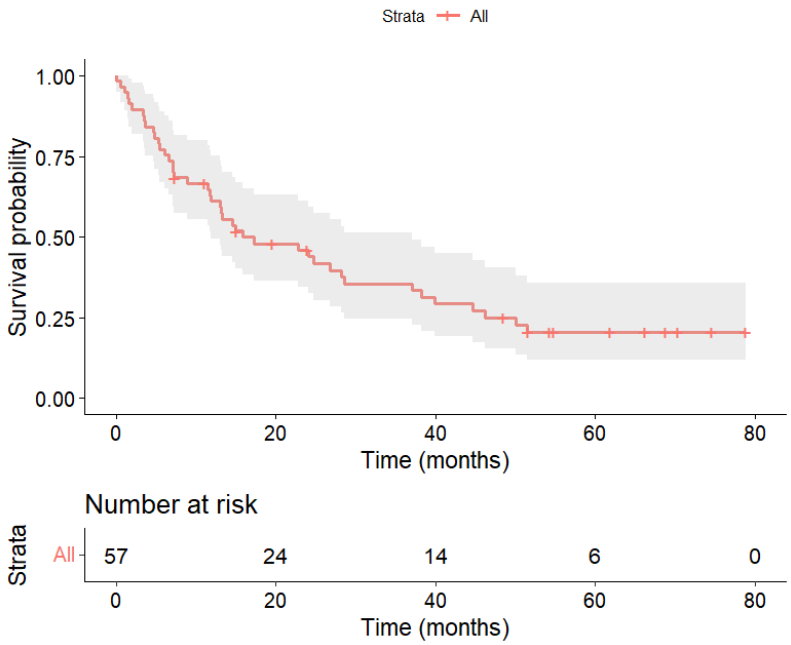
Additionally, the matched CM 142 data for the PF-to-PD transition ($p_{1,2}$) was compared against the PF-to-PD transition ($p_{1,2}$) estimated using CM 8HW data in order to validate that the matching process had been carried out correctly. Both KM curves overlapped, implying that the matched CM 142 data is comparable to CM 8HW.

Based on the above, it is recommended that the unmatched CM 142 is used to estimate PD-to-death transition ($p_{2,3}$) in the base case. However, the results for the matched and unmatched data are presented here and can be used in the model should the user wish.

D.5.2 Estimation of the PD-to-death transition ($p_{2,3}$) based on unmatched CM 142 data

For the unmatched CM 142 data, there were a total of 57 patients included in this transition, all of which received NIVO+IPI (cohorts 2 and 3) (Figure 53). This included patients in CM 142 that died after being diagnosed with progressed disease. The median time to death after experiencing progressed disease (in months) was 15.9 (95% CI, 11.8-37.1), and the 1-year death-free probability after experiencing progressed disease was 0.61 (95% CI, 0.50-0.75).

Figure 55. KM curve for the PD-to-Death transition ($p_{2,3}$) estimated based on unmatched CM 142 data



CM = CheckMate; KM = Kaplan-Meier; PD = Progressed Disease.

D.5.2.1 Evaluation of statistical fit

Standard parametric models were fit to the unmatched CM 142 data to estimate the PD-to-death transition ($p_{2,3}$). Model fits were then extrapolated beyond the observed period of the CM 142 trial to derive an estimate of the long-term transition probabilities for PD-to-death ($p_{2,3}$). The AIC values for all fits can be found in Table 30.

Table 30. AIC values for all standard parametric fits for the PD-to-death transition ($p_{2,3}$) fit to unmatched CM 142 data

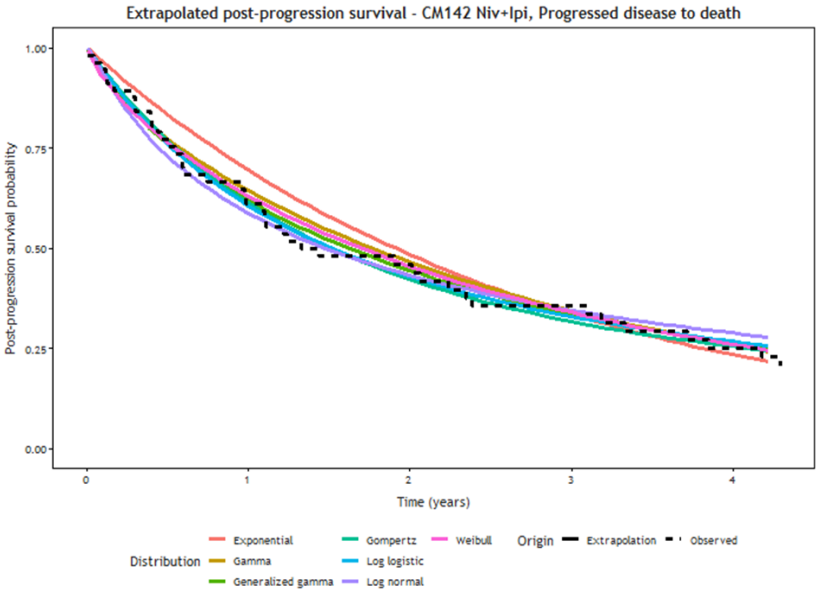
PD-to-death Transition	CM 142 NIVO+IPI AIC	CM 142 NIVO+IPI BIC
Exponential	666.7	668.7
Gamma	665.0	669.1
Generalised gamma	665.8	672.0
Gompertz	**663.2**	667.3
Log-logistic	663.5	667.6
Log-normal	667.0	671.1
Weibull	664.4	668.4

AIC = Akaike information criteria; CM = CheckMate; IPI = ipilimumab; NIVO = nivolumab; PD = Progressed Disease.

D.5.2.2 Evaluation of visual fit

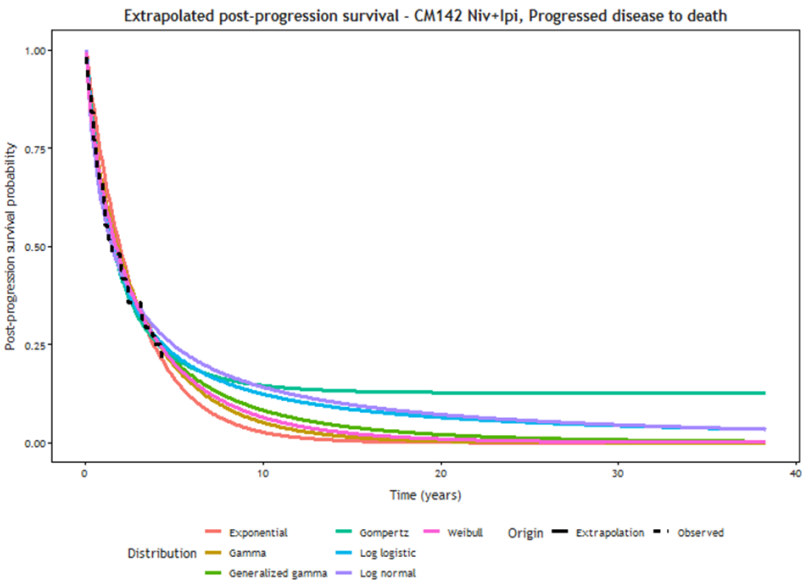
The model extrapolations can be found in Figure 54 and Figure 55.

Figure 56. Standard parametric fits of the PD-to-death transition ($p_{2,3}$) for unmatched CM 142 data, extrapolated up to the observed trial period



CM = CheckMate; PD = Progressed Disease.

Figure 57. Standard parametric fits of the PD-to-Death transition ($p_{2,3}$) for unmatched CM 142 data, extrapolated beyond the observed trial period



CM = CheckMate; PD = Progressed Disease.

D.5.2.3 Evaluation of hazard function

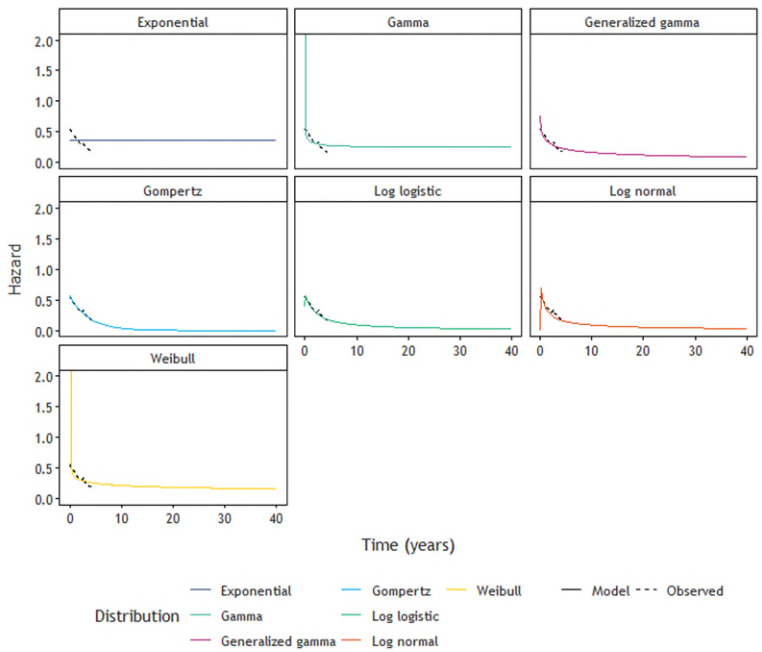
The landmark survival values can be found in Table 31. The corresponding smoothed hazard plots for these extrapolations can be found in Figure 56.

Table 31. Landmark survival estimates (years) of the standard parametric fits of the PD-to-death transition ($p_{2,3}$) for the unmatched CM 142 data

	Median TTP	1 year	5 years	10 years	20 years
Observed	15.8	0.61	0.20	NR	NR
Exponential	23.0	0.70	0.16	0.03	0.00
Gamma	21.2	0.64	0.20	0.05	0.00
Generalised gamma	19.4	0.62	0.21	0.08	0.02
Gompertz	18.4	0.61	0.22	0.15	0.13
Log-logistic	18.5	0.61	0.23	0.12	0.06
Log-normal	17.5	0.59	0.25	0.14	0.07
Weibull	20.3	0.63	0.20	0.06	0.01

CM = CheckMate; NR = not reported; PD = Progressed Disease; TTP = time to progression.

Figure 58. Smoothed hazard plots of the standard parametric fits to the PD-to-death transition ($p_{2,3}$) for unmatched CM 142, extrapolated beyond the observed trial period



CM = CheckMate; PD = Progressed Disease.

D.5.2.4 Summary and discussion

Of the seven parametric models fit, the Gompertz can be excluded immediately based on unrealistic extrapolations as seen in Figure 55, where it predicts an unrealistically high long-term postprogression survival. The exponential also fits poorly from 0-2 years,

estimating too high of PPS. Looking at the AIC values of the remaining candidate fits in Table 30, the log-logistic (663.5), Weibull (664.4), and gamma (665.0) fits had the lowest values. Among these, the log-logistic had the most optimistic long-term extrapolations (Figure 55 and Table 31) but the lowest median PPS at 18.5 months (95% CI, 12.0, 28.6) which was closest to the observed of 15.8 months (95% CI, 11.8, 37.2). 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 55. At 1 year and 5 years, all three models behave comparably to the observed data. With regards to the smoothed hazard plots shown in Figure 56, the log-logistic, Gompertz, and log-normal distributions have better fits to the observed hazards. Due to its slightly lower AIC value, the log-logistic model was chosen as the base case for the economic model.

D.5.3 Estimation of PD-to-Death transition ($p_{2,3}$) based on matched CM 142 data

To support the decision to use the unweighted CM 142 data for this transition, the above outlined fitting and model selection process was repeated using the matched and weighted cohort.

D.5.3.1 Evaluation of statistical fit

The AIC values for all fits can be found in Table 32.

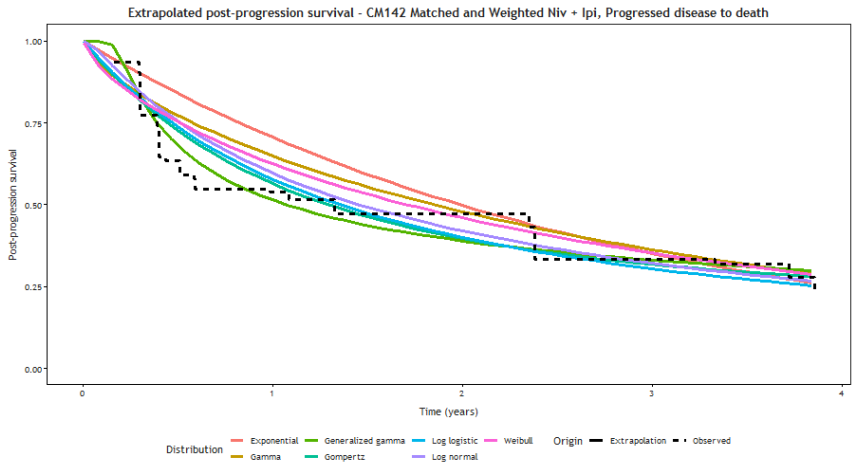
Table 32. AIC values for all standard parametric fits for the PD-to-death transition ($p_{2,3}$) fit to matched and weighted CM 142 data

PD-to-death Transition	CM 142 NIVO+IPI AIC
Exponential	284.2
Gamma	284.2
Generalised gamma	**273.2**
Gompertz	279.3
Log-logistic	279.8
Log-normal	278.5
Weibull	283.1

D.5.3.2 Evaluation of visual fit

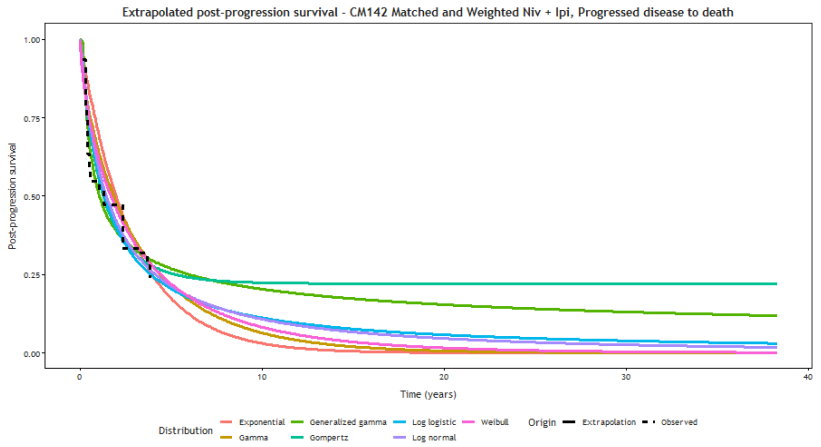
Extrapolated survival curves for matched CM 142 data are presented in Figure 57 and Figure 58.

Figure 59. Standard parametric fits of the PD-to-death transition ($p_{2,3}$) for matched and weighted CM 142 data, extrapolated up to the observed trial period



CM = CheckMate; PD = Progressed Disease.

Figure 60. Standard parametric fits of the PD-to-death transition ($p_{2,3}$) for matched and weighted CM 142 data, extrapolated beyond the observed trial period



CM = CheckMate; PD = Progressed Disease.

D.5.3.3 Evaluation of hazard function

The landmark survival values can be found in Table 33. The corresponding smoothed hazard plots for these extrapolations can be found in Figure 59.

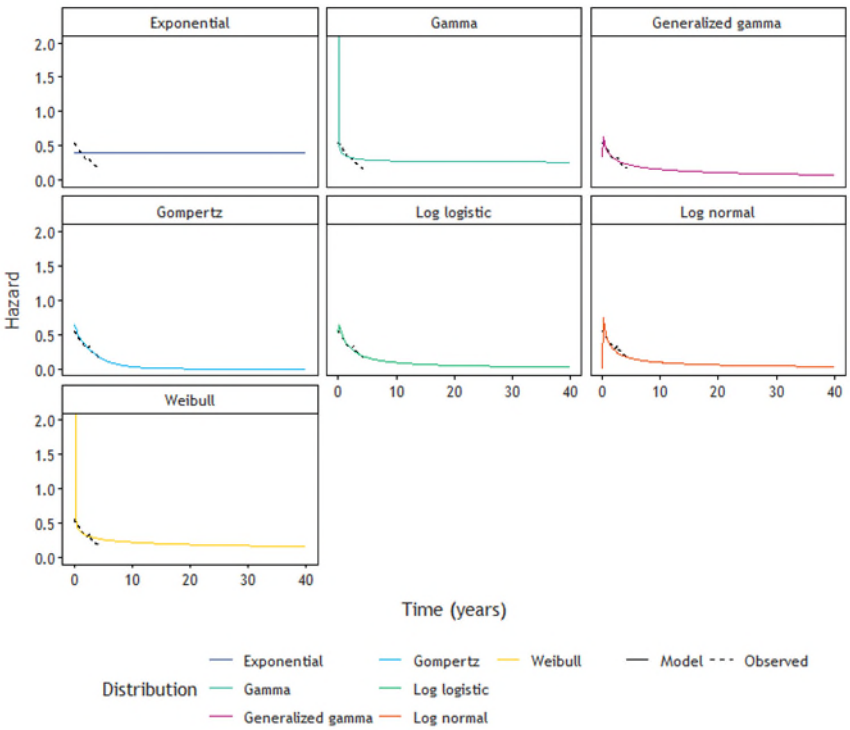
Table 33. Landmark survival estimates (years) of the standard parametric fits of the PD-to-death transition ($p_{2,3}$) for the matched and weighted CM 142 data

	Median TTP	1 year	5 years	10 years	20 years
Observed	15.9	0.54	0.24	NR	NR
Exponential	24.0	0.71	0.18	0.03	0
Gamma	22.1	0.65	0.22	0.06	0.01

	Median TTP	1 year	5 years	10 years	20 years
Generalised gamma	12.9	0.51	0.27	0.20	0.15
Gompertz	15.7	0.56	0.25	0.22	0.22
Log-logistic	16.6	0.58	0.21	0.11	0.06
Log-normal	17.5	0.60	0.21	0.11	0.05
Weibull	20.3	0.62	0.22	0.08	0.02

CM = CheckMate; NR = not reported; PD = Progressed Disease; TTP = time to progression.

Figure 61. Smoothed hazard plots of the standard parametric fits to the PD-to-death transition ($p_{2,3}$) for matched and weighted CM 142, extrapolated beyond the observed trial period



CM = CheckMate; PD = Progressed Disease.

D.5.3.4 Summary and discussion

Among the considered models, the generalised gamma had the lowest AIC as well as the best fit to the shape of the observed data, particularly in the first year as it was the only model that captured the initial drop in postprogression survival (Figure 57). Its long-term extrapolations (Figure 58) were more optimistic than most models; however, they were not as optimistic as those from the Gompertz model. With regards to the smoothed hazards, the generalised gamma, log-logistic, and Gompertz models had a better fit to the observed hazards. However, based on all of the factors above, ultimately the

generalised gamma model made the best fit to the matched and weighted CM 142 data for the PD-to-death transition ($p_{2,3}$).

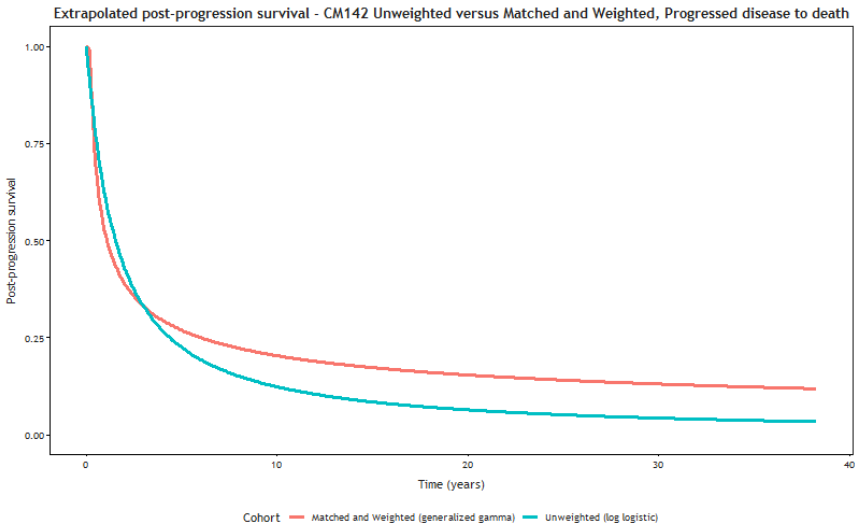
D.5.4 Comparison between unmatched and matched CM 142 data

Finally, the best-fitting parametric curves from both the unmatched and the matched and weighted cohorts for the PD-to-death transition ($p_{2,3}$) were plotted together to compare their long-term extrapolations, which can be seen in Figure 60. The generalised gamma curve was fit to the matched and weighted CM 142 data for the PD-to-death transition ($p_{2,3}$) while the log-logistic curve fit to the unmatched CM 142 data.

For the unweighted cohort, the long-term extrapolations are less optimistic overall and more in line with what would be expected for the PD-to-death transition ($p_{2,3}$) up to 40 years. The two models behave comparably in years 1 to 5, so the majority of the difference is observed in the extrapolated period.

Given the high variability in the matched and weighted cohort due to the small ESS, it is a safer and more conservative choice to use the unweighted cohort fitted by a log-logistic model for this transition.

Figure 62. Comparison of best extrapolated curves fit to unweighted versus matched and weighted CM 142 data for the PD-to-Death transition ($p_{2,3}$)



CM = CheckMate; PD = Progressed Disease.

D.6 Validation

To validate the extrapolated results produced for each transition as previously outlined, the best model fit at each transition was selected based on the model selection algorithm outlined in Palmer et al. (2023)[31] as well as via statistical tests such as AIC. Besides these methods, standard parametric model fits were also compared against survival curves generated from external data sources described in Table 34.

Table 34. An outline of external validation sources used to aid in standard parametric model selection

Outcome	Validation source
Extrapolated TTP curves from CM 8HW	Tougeron et al. (2020)[34]
OS outputs generated from the CEM	KN-177[9] and CM 142 data[8]
PFS curve generated from unweighted CM 142 data	PFS curve generated from CM 8HW data[1]

CEM = cost-effectiveness model; CM = CheckMate; KN = KEYNOTE; NIVO = nivolumab; OS = overall survival; PFS = progression-free survival; TTP = time to progression.

D.6.1 Validation for PF-to-PD transition

The extrapolated PF-to-PD transition ($p_{1,2}$) estimated for the three best-fitting models for the chemotherapy arm in the CM 8HW data were validated against Tougeron et al. (2020)[34] and chemotherapy data from KN-177 published by Diaz et al. (2022)[9].

Tougeron et al. (2020)[34] collected PFS and OS data of patients receiving 1L chemotherapy for stage IV MSI-H/dMMR CRC in France for over 10 years. As such, extrapolated curves generated for the chemotherapy arm in CM 8HW can be compared against those from Tougeron et al. (2020)[34] to determine which is the best-fitting model. Similarly, KN-177 evaluated the effect of PEMBRO versus chemotherapy in 1L MSI-H/dMMR patients; thus, their treatment arm and patient population with respect to the chemotherapy arm are comparable to that of CM 8HW.

Therefore, extrapolated curves generated for the chemotherapy arm in CM 8HW can also be compared with those produced from KN-177 to aid in model selection. The landmark survival values are presented in Table 35.

The median estimated TTP for the CM 8HW 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 CM 8HW extrapolations encompass the estimated 3-year PFS from Diaz et al. (2022)[9]. At 5-years, the generalised gamma extrapolated fit of PF to PD for CM 8HW validates the best to Diaz et al. (2022)[9].

Table 35. Landmark survival values of the three best-fitting standard parametric models for the CM 8HW chemotherapy arm, compared with extrapolated results fromTougeron et al. (2020)[34] and Diaz et al. (2022)[9]

	CM 8HW chemotherapy				Tougeron et al. (2020)[34] 1L chemo PFS	KN-177 chemo PFS
	Observed	Log-normal	Generalised gamma	Log-logistic		
Median TTP, years (95% CI)	7.4 (5.6-10.9)	8.3 (6.5-10.2)	7.4 (5.5-10.2)	7.4 (6.5-10.2)	6.0 (5.0-7.8)	8.2 (6.2-10.3)
1-year PF probability	32% (22%-47%)	35% (24%-45%)	35% (25%-46%)	33% (22%-42%)	-	-
3-year PF probability	NR	8% (3%-15%)	12% (4%-24%)	7% (3%-13%)	-	13%
5-year PF probability	NR	3% (1%-7%)	7% (1%-18%)	3% (1%-7%)	-	8%

CI = confidence interval; CM = CheckMate; KN = KEYNOTE; NR = not reported; PFS = progression-free survival; TTP = time to progression.

D.6.2 Validation of the matched CM 142 data

To validate our results, the matched and reweighted CM 142 data was plotted against CM 8HW data for the PF-to-PD transition ($p_{1,2}$) as shown in Figure 61. Although the estimated TTP of the weighted CM 142 data is higher compared with the CM 8HW data, the estimated median TTP of the weighted CM 142 arm is 38.9 (95% CI, 19.1-not reached), which falls within the 95% confidence interval estimate of the median TTP for the NIVO+IPI arm in CM 8HW (NR; 95% CI, 38.4-not reached). Furthermore, difference in estimated TTP may be due to the low ESS produced in the matched and reweighted CM 142 data, as well as the factors outlined in Appendix D.2.1.

Figure 63. KM curves of the PF-to-PD transition ($p_{1,2}$) for the matched and reweighted CM 142 data, compared against PF-to-PD transition ($p_{1,2}$) for the unmatched CM 142 and CM 8HW

CM = CheckMate; KM = Kaplan-Meier; PD = Progressed Disease; PF = Progression Free.

Despite the discrepancy in TTP estimates, the 95% confidence intervals of both the CM 8HW and reweighted CM 142 KM curves overlap with each other, implying that both are comparable. Crucially, the KM curves produced by the unmatched CM 142 data also overlap with the matched and reweighted CM 142 data for the PF-to-PD transition ($p_{1,2}$), suggesting that both curves are comparable. This aligns with what was observed in Appendix D.5.1 with regards to the PD-to-death transition ($p_{2,3}$).

Appendix E. Serious adverse events

All SAEs that occurred in the CM 8HW study are reported in Table 36.

Table 36. Serious adverse events reported in any participant (all first-line treated population)

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
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[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
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[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
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[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
[redacted]						
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[redacted]						
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[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
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System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
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[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
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[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]						
[redacted]						
[redacted]						
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[redacted]						

System organ class (%) Preferred term (%)	NIVO+IPI (N = 200)			Chemotherapy (N = 88)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CTC Version 5.0

Includes events reported between first dose and 30 days after last dose of study therapy. Excludes data collected on or after first crossover dose date.

Only first-line subjects are included for Arm B and Arm C.

Appendix F. Health-related quality of life

All content is in the main dossier.

Appendix G. Probabilistic sensitivity analyses

Table 37 lists the distribution for each set of model inputs varied in the PSA and provides a brief description of each. Distributions selected follow the logical bounds allowed for each parameter. For example, probabilities must be between 0 and 1, so the beta distribution is used, which holds the same bounds. Similarly, costs incurred cannot be negative. Thus, gamma distribution with bounds between 0 and positive infinity is used in the probabilistic sampling.

Table 37. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Patient Population				
% Female	53.80%	32.60%	74.30%	Beta
Age at start (years)	60.90	59.29	62.51	Normal
Average weight	70.50	68.46	72.54	Normal
Mean body surface area (m^2)	1.78	1.75	1.81	Normal
Resource Use				
Liver function test – units used	1.15	0.74	1.64	Gamma
CT scan – units used	0.30	0.19	0.43	Gamma
Consultation outpatient appointment -units used	2.00	1.29	2.86	Gamma
Progressed disease care – Consultation outpatient appointment – units used	0.167	0.11	0.24	Gamma
Best supportive care – CT scan – units used	0.167	0.11	0.24	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Mean Time in Progressed State				
NIVO+IPI	1,271.07	772.82	1,769.32	Normal
PEMBRO	1,271.07	772.82	1,769.32	Normal
Mean time on treatment (mean doses)				
NIVO+IPI Induction	3.61	2.19	5.03	Normal
NIVO+IPI maintenance	11.90	7.24	16.56	Normal
PEMBRO	16.09	9.78	22.39	Normal
Chemotherapy (subsequent treatment)	11.00	6.69	15.31	Normal
HSUV				
Progression free	0.82	0.80	0.84	Beta
Progressed disease	0.79	0.76	0.82	Beta
Costs				
IV – administration costs	1,561.00	1,010.20	2,229.74	Gamma
Complex IV – administration costs	1,561.00	1,010.20	2,229.74	Gamma
Liver function test costs	73.00	47.24	104.27	Gamma
CT scan costs	2,021.00	1,307.88	2,886.80	Gamma
Consultation outpatient appointment costs	1,561.00	1,010.20	2,229.74	Gamma
FOLFIRI - Cost per administration	4,190.00	2,711.55	5,985.01	Gamma
FOLFIRI + cetuximab -Cost per administration	16,594.11	10,738.83	23,703.09	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Mono IO therapy	60837.50	39370.82	86900.52	Gamma
Combo IO therapy	39669.46	25671.99	56664.02	Gamma
AE costs - Hepatitis	1,947.00	1,260.00	2,781.10	Gamma
AE costs - Neutropenia	2,111.00	1,366.13	3,015.36	Gamma
AE costs - Rash	1,625.00	1,051.61	2,321.16	Gamma
AE costs - Diarrhoea/colitis	1,561.00	1,010.20	2,229.74	Gamma
AE costs - Adrenal insufficiency	1,847.00	1,195.28	2,638.26	Gamma
AE costs - Hyperthyroidism	1,847.00	1,195.28	2,638.26	Gamma
AE costs - Hypophysitis	1,847.00	1,195.28	2,638.26	Gamma
AE costs - Asthenia	5,103.00	3,302.39	7,289.15	Gamma
AE costs - Decreased neutrophil count	2,111.00	1,366.13	3,015.36	Gamma
AE costs - Hypertension	1,561.00	1,265.43	1,887.13	Gamma
AE costs - Increased Lipase	1,561.00	1,010.20	2,229.74	Gamma
AE costs - Pneumonia	43,907.00	28,414.30	62,716.93	Gamma
Dose Intensity				
FOLFIRI				
Irinotecan	100%	100%	100%	Beta
Fluorouracil bolus	100%	100%	100%	Beta
Fluorouracil infusion	100%	100%	100%	Beta
Leucovorin	100%	100%	100%	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
FOLFIRI + cetuximab				
Irinotecan	100%	100%	100%	Beta
Fluorouracil bolus	100%	100%	100%	Beta
Fluorouracil infusion	100%	100%	100%	Beta
Leucovorin	100%	100%	100%	Beta
Cetuximab	100%	100%	100%	Beta
Mean time on subsequent treatment (Weeks)				
FOLFIRI	20.16	13.05	28.80	Gamma
FOLFIRI + cetuximab	20.16	13.05	28.80	Gamma
Mono IO therapy	104.36	67.53	149.06	Gamma
Combo IO therapy	104.36	67.53	149.06	Gamma
Incidence of grade 3-4 adverse event: NIVO+IPI				
Hepatitis	3.00%	1.94%	4.28%	Beta
Neutropenia	1.00%	0.65%	1.43%	Beta
Rash	1.50%	0.97%	2.14%	Beta
Diarrhoea/colitis	4.50%	2.90%	6.42%	Beta
Adrenal insufficiency	3.50%	2.26%	4.99%	Beta
Hyperthyroidism	1.50%	0.97%	2.14%	Beta
Hypophysitis	2.50%	1.62%	3.57%	Beta
Asthenia	2.00%	1.29%	2.86%	Beta
Decreased neutrophil count	0.50%	0.32%	0.71%	Beta
Hypertension	1.50%	0.97%	2.14%	Beta
Increased Lipase	0.00%	0.00%	0.00%	Beta
Pneumonia	2.00%	1.29%	2.86%	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Incidence of grade 3-4 adverse event: PEMBRO				
Hepatitis	2.61%	1.69%	3.73%	Beta
Neutropenia	0.70%	0.45%	1.00%	Beta
Rash	1.31%	0.85%	1.87%	Beta
Diarrhoea/colitis	3.27%	2.11%	4.66%	Beta
Adrenal insufficiency	1.31%	0.85%	1.87%	Beta
Hyperthyroidism	0.00%	0.00%	0.00%	Beta
Hypophysitis	0.00%	0.00%	0.00%	Beta
Asthenia	2.00%	1.29%	2.86%	Beta
Decreased neutrophil count	0.00%	0.00%	0.00%	Beta
Hypertension	7.20%	4.64%	10.26%	Beta
Increased Lipase	0.00%	0.00%	0.00%	Beta
Pneumonia	3.30%	2.13%	4.71%	Beta
Duration of grade 3-4 adverse event (in number of cycles)				
Hepatitis	0.25	0.16	0.36	Gamma
Neutropenia	0.25	0.16	0.36	Gamma
Rash	0.25	0.16	0.36	Gamma
Diarrhoea/colitis	0.25	0.16	0.36	Gamma
Adrenal insufficiency	3.86	2.50	5.51	Gamma
Hyperthyroidism	3.86	2.50	5.51	Gamma
Hypophysitis	3.86	2.50	5.51	Gamma
Asthenia	0.25	0.16	0.36	Gamma
Decreased neutrophil count	0.25	0.16	0.36	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Hypertension	0.25	0.16	0.36	Gamma
Increased Lipase	0.25	0.16	0.36	Gamma
Pneumonia	0.25	0.16	0.36	Gamma
Disutility of grade 3-4 adverse event				
Hepatitis	-0.20	-0.20	-0.20	Beta
Neutropenia	-0.06	-0.06	-0.06	Beta
Rash	-0.04	-0.04	-0.04	Beta
Diarrhoea/colitis	-0.09	-0.09	-0.09	Beta
Adrenal insufficiency	-0.20	-0.20	-0.20	Beta
Hyperthyroidism	-0.07	-0.07	-0.07	Beta
Hypophysitis	-0.20	-0.20	-0.20	Beta
Asthenia	-0.08	-0.08	-0.08	Beta
Decreased neutrophil count	-0.07	-0.07	-0.07	Beta
Hypertension	-0.07	-0.07	-0.07	Beta
Increased Lipase	-0.08	-0.08	-0.08	Beta
Pneumonia	-0.20	-0.20	-0.20	Beta

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator

An SLR was conducted to describe and characterise the landscape of evidence published between 2009 and 2024, on the comparative efficacy and safety of 1L treatments in patients with mCRC with MSI-H/dMMR status.[36] Methods for conducting this SLR adhered to the standard methodologies for conducting and reporting systematic reviews as recommended by the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions.[37] are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[38]

To capture all relevant peer-reviewed published information, databases and other sources presented in Table 38, Table 39, and Table 40 were searched on 2 April 2024.

Table 38. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid® platform	2009-2024	02.04.2024
MEDLINE®	Ovid® platform	2009-2024	02.04.2024
EBM Central	Ovid® platform	2009-2024	02.04.2024

Source: BMS data on file (2024)[36]

Table 39. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	ClinicalTrials.gov	Manual search	02.04.2024
clinicaltrialsregister.eu	clinicaltrialsregister.eu	Manual search	02.04.2024

Source: BMS data on file (2024)[36]

Table 40. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Association for Cancer Research (AACR)	Conference proceedings (2022-2024)	Manual search	N/A	02.04.2024
American Society of Clinical Oncology (ASCO)	Conference proceedings (2022-2024)	Manual search	N/A	02.04.2024
American Society of Clinical Oncology	Conference proceedings (2022-2024)	Manual search	N/A	02.04.2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Gastrointestinal Cancers (ASCO GI)				
American Society of Colon and Rectal Surgeons (ASCRS)	Conference proceedings (2022-2024)	Manual search	N/A	02.04.2024
European Society of Coloproctology (ESC)	Conference proceedings (2022-2024)	Manual search	N/A	02.04.2024
European Society for Medical Oncology (ESMO)	Conference proceedings (2022-2024)	Manual search	N/A	02.04.2024
European Society for Medical Oncology Gastrointestinal Cancers (ESMO GI)	Conference proceedings (2022-2024)	Manual search	N/A	02.04.2024

N/A = not available

Source: BMS data on file (2024)[36]

Additionally, bibliographies of relevant SLRs/meta-analyses captured in the electronic searches were screened for additional primary records that were not retrieved via electronic searches.

H.1.1 Search strategies

The search was tailored to each individual database and combined specific MSI-H/dMMR mCRC terms with specific study design search terms, presented in Table 41, Table 42, and Table 43. The search terms used a combination of free text searching (multipurpose terms) and 'subject headings' (common descriptive terms assigned to publications as part of the database indexing).[36]

A summary of the key search terms is outlined below:

- Patient Population: Specific Emtree (Embase), Medical Subject Heading (MeSH) (Medline) and free text terms to identify relevant MSI-H/dMMR mCRC studies (e.g., microsatellite instability/ and metastatic colorectal cancer/ for Embase) were used to ensure that the most relevant data is identified.
- Study Design: SIGN RCT search filters were applied to identify relevant study designs (e.g., Clinical Trial/ for Embase). Exclusion filters were applied to remove study designs that are not of interest (e.g., case study/ or animal/ for Embase).

Table 41. Search strategy for Embase (run on 2 April 2024)

No.	Query	Results
#1	microsatellite instability/	22,207

No.	Query	Results
#2	("MSI-H" or "microsatellite instability high" or "MSI-high").ti,ab,kw.	6,330
#3	mismatch repair/	19,383
#4	(("dMMR" or "mismatch repair deficiency" or "mismatch repair deficient" or deficien$) adj2 mismatch repair).ti,ab,kw.	5,623
#5	"MSI-H/dMMR".ti,ab,kw.	336
#6	or/1-5	38,250
#7	exp colorectal carcinoma/ or exp metastatic colorectal cancer/ or exp metastatic colon cancer/	104,653
#8	(((advance* or metasta*) adj3 (colorectal* or colo-rectal*)) or mCRC).ti,ab.	54,713
#9	7 or 8	134,563
#10	6 and 9	5,200
#11	clinical trial/	1,080,602
#12	Randomized Controlled Trial/	815,300
#13	controlled clinical trial/	472,751
#14	multicenter study/	388,751
#15	Phase 3 clinical trial/	74,769
#16	Phase 4 clinical trial/	7,054
#17	exp RANDOMIZATION/	99,475
#18	Single Blind Procedure/	54,175
#19	Double Blind Procedure/	217,536
#20	Crossover Procedure/	77,494
#21	PLACEBO/	411,042
#22	randomi?ed controlled trial$.tw.	342,296
#23	rct.tw.	57,064
#24	(random$ adj2 allocat$).tw.	56,953
#25	single blind$.tw.	32,886

No.	Query	Results
#26	double blind$.tw.	250,745
#27	((treble or triple) adj blind$).tw.	2,070
#28	placebo$.tw.	377,204
#29	Prospective study/	911,815
#30	or/11-29	3,035,238
#31	10 and 30	724
#32	(conference or conference abstract or conference review).pt.	5,884,261
#33	limit 32 to yr="2009-2021"	4,565,611
#34	31 not 33	477
#35	(exp animal/ or nonhuman/) not exp human/	7,293,332
#36	(book or chapter or editorial or erratum or letter or note or short survey or tombstone or comment).pt.	3,845,831
#37	Case Study/	100,118
#38	case report.tw.	564,205
#39	or/35-38	11,580,227
#40	34 not 39	465
#41	limit 40 to yr="2009 -Current"	436
#42	limit 41 to english language	433

Table 42. Search strategy for Medline (run on 2 April 2024)

No.	Query	Results
#1	microsatellite instability/	4,970
#2	("MSI-H" or "microsatellite instability high" or "MSI-high").ti,ab,kw.	3,195
#3	DNA mismatch repair/	4,198
#4	(("dMMR" or "mismatch repair deficiency" or "mismatch repair deficient" or deficien$) adj2 mismatch repair).ti,ab,kw.	3,521
#5	"MSI-H/dMMR".ti,ab,kw.	159

No.	Query	Results
#6	or/1-5	11,333
#7	exp colorectal neoplasms/	244,581
#8	(((advance* or metasta*) adj3 (colorectal* or colo-rectal*)) or mCRC).ti,ab.	33,177
#9	7 or 8	252,175
#10	6 and 9	5,852
#11	clinical trial/	539,691
#12	Randomized Controlled Trial/	610,515
#13	controlled clinical trial/	95,520
#14	multicenter study/	344,453
#15	Clinical Trials, Phase III as Topic/	11,342
#16	Clinical Trials, Phase IV as Topic/	392
#17	exp random allocation/	107,068
#18	Single-Blind Method/	33,346
#19	Double-Blind Method/	177,918
#20	Cross-Over Studies/	56,407
#21	Placebo Effect/	5,209
#22	randomi?ed controlled trial$.tw.	266,095
#23	rct.tw.	33,912
#24	(random$ adj2 allocat$).tw.	46,012
#25	single blind$.tw.	24,318
#26	double blind$.tw.	175,244
#27	((treble or triple) adj blind$).tw.	1,657
#28	placebo$.tw.	254,965
#29	Prospective Studies/	683,775
#30	or/11-29	2,055,398

No.	Query	Results
#31	10 and 30	525
#32	exp animals/ not exp humans/	5,208,585
#33	(editorial or letter or comment).pt.	2,235,908
#34	exp Case Reports/ or exp Letter/ or exp Editorial/	4,098,793
#35	case report.tw.	421,658
#36	or/32-35	9,555,312
#37	31 not 36	517
#38	limit 37 to yr="2009 -Current"	438
#39	limit 38 to english language	426

Table 43. Search strategy for EBM Central (run on 2 April 2024)

No.	Query	Results
#1	microsatellite instability/	107
#2	("MSI-H" or "microsatellite instability high" or "MSI-high").ti,ab,kw.	285
#3	DNA mismatch repair/	73
#4	(("dMMR" or "mismatch repair deficiency" or "mismatch repair deficient" or deficien$) adj2 mismatch repair).ti,ab,kw.	228
#5	"MSI-H/dMMR".ti,ab,kw.	42
#6	or/1-5	484
#7	exp colorectal neoplasms/	13,248
#8	(((advance* or metasta*) adj3 (colorectal* or colo-rectal*)) or mCRC).ti,ab.	7,318
#9	7 or 8	17,478
#10	6 and 9	274
#11	clinical trial/	100
#12	Randomized Controlled Trial/	92
#13	controlled clinical trial/	9

No.	Query	Results
#14	multicenter study/	13
#15	Clinical Trials, Phase III as Topic/	2,361
#16	Clinical Trials, Phase IV as Topic/	93
#17	exp random allocation/	26,044
#18	Single-Blind Method/	27,263
#19	Double-Blind Method/	170,426
#20	Cross-Over Studies/	47,745
#21	Placebo Effect/	2,239
#22	randomi?ed controlled trial$.tw.	282,150
#23	rct.tw.	50,886
#24	(random$ adj2 allocat$).tw.	67,527
#25	single blind$.tw.	41,152
#26	double blind$.tw.	298,470
#27	((treble or triple) adj blind$).tw.	3,302
#28	placebo$.tw.	385,317
#29	Prospective Studies/	129,266
#30	or/11-29	921,618
#31	10 and 30	51
#32	exp animals/ not exp humans/	3,717
#33	(editorial or letter or comment).pt.	17,695
#34	exp Case Reports/ or exp Letter/ or exp Editorial/	0
#35	case report.tw.	3,049
#36	or/32-35	24,445
#37	31 not 36	51

No.	Query	Results
#38	limit 37 to yr="2009 -Current" [Limit not valid in DARE; records were retained]	46
#39	limit 38 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCA,CLCMR; records were retained]	45

H.1.2 Systematic selection of studies

This review used prespecified eligibility criteria following the PICOTS framework (Population, Intervention, Comparator, Outcomes, Timeframe, Study design). Studies meeting the PICOTS criteria were included in the SLR. Specific criteria are outlined in Table 44.[36]

Table 44. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaptation
Population	Adults (aged ≥ 18 years) with untreated MSI-H/dMMR mCRC status	▪ Children and young people ▪ Adults with mCRC without MSI-H/dMMR status ▪ Studies which include MSI-H/dMMR population but are not well-powered to adequately collect data in MSI-H/dMMR population (at full-text phase) ▪ Studies which do not include subgroup analysis in adults with MSI-H/dMMR mCRC status (at full-text phase)	N/A
Intervention	Any 1L therapy administered in patients with MSI-H/dMMR mCRC, including off-licence administration	N/A	NIVO+IPI is the intervention relevant to this submission
Comparators	Any 1L treatment.	N/A	PEMBRO is the only comparator relevant in Denmark and included in the submission

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaptation
Outcomes	Survival: ▪ Overall survival (OS) ▪ Progression-free survival (PFS) ▪ Time to progression (TTP) ▪ Recurrence-free survival (RFS) ▪ Disease-free survival (DFS) ▪ Time to treatment failure (TTTF) Response: ▪ Overall response rate (ORR) ▪ Complete response (CR) ▪ Partial response (PR) ▪ Stable disease (SD) ▪ Duration of response (DoR) Safety: ▪ Toxicity and tolerability ▪ Total adverse events (AEs) ▪ Total treatment-related AEs ▪ Total serious AEs (SAEs) ▪ Total treatment-related SAEs ▪ Withdrawal ▪ Mortality ▪ Treatment-related mortality	Economic outcomes: ▪ Healthcare resource utilisation outcomes ▪ Direct costs ▪ Indirect costs ▪ Productivity loss ▪ Other economic outcomes such as premature death, cost-effectiveness of therapies, mean excess treatment cost per patient, mean total cumulative cost per patient, mean total cost per patient and total lifetime standard-of-care costs. Humanistic outcomes: ▪ Health-related quality of life (HRQoL) and patient reported outcomes, including but not limited to: EQ-5D, QLQ-C30, SF-36, HADS)	N/A
Timeframe	2009[a] – present for database searches; 2022 – present for conference proceedings		
Study design/publication type	▪ Randomised controlled trials (Phase 2-4) ▪ Non-randomised clinical trials ▪ SLR/meta-analyses.[b]	▪ Phase 1 clinical trials (dose escalation, dose finding methods) ▪ Observational studies: — Cohort studies — Case series — Case reports — Case-control studies — Case studies	N/A

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaptation
		– Database studies ▪ Comments and opinions ▪ Letters and editorials ▪ Book or book chapters ▪ News or newspaper article ▪ Guidelines /consensus statements ▪ Articles investigating in vitro, animal, fetal, molecular, genetic, pathologic, or pharmacokinetic/ pharmacodynamic outcomes ▪ Narrative reviews, non-systematic literature reviews	
Language restrictions	Studies published in English language	Non-English language	

[a] Timeframe started from 2009 to align with the first instances of literature being published containing MSI-H/dMMR biomarker defined populations.[39]

[b] Relevant SLRs/meta-analyses are to be included for bibliographic checks for primary publications that were not retrieved via other search methods. Once reviewed at the full-text screening stage, SLRs/meta-analyses will be excluded from this review.

Source: BMS data on file (2024)[36]

H.1.2.1 Data extraction

A data extraction form was developed in Microsoft Excel of which articles were extracted into by a single reviewer, and then quality checked by a second reviewer. The data extraction form included study information, treatment characteristics, patient characteristics, survival, response, and safety outcomes. Data were extracted from full-text publications and conference abstracts. All relevant full-text and non-full-text references were linked to the original primary source, where appropriate.[36]

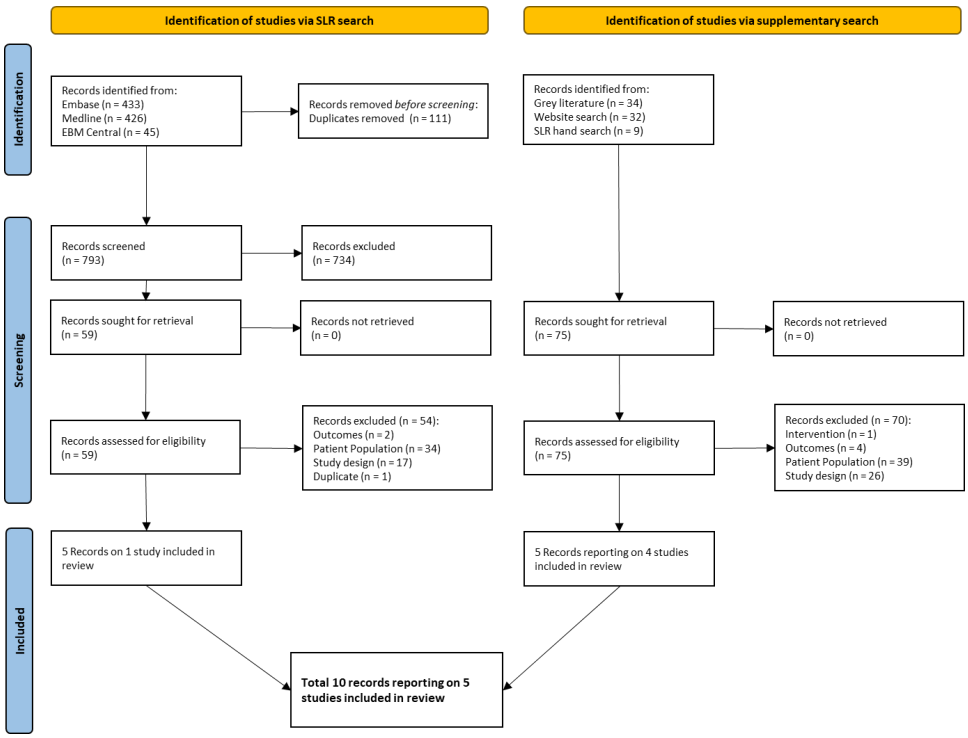
H.1.2.2 Risk of bias

As highlighted in Table 44, randomised controlled trials and non-randomised clinical trials were included in the review. The Cochrane Collaboration's tool for assessing risk of bias (ROB) in randomised trial (version 2) was used to assess the internal validity of the studies. The ROB checklist was included in the data extraction form.[40] ROB was assessed by a single reviewer, and then quality checked by a second reviewer.[36]

H.1.3 Search results

Following deduplication, the database searches retrieved a total of 793 records. Following abstract screening, 59 potential records were identified for full-text screening, resulting in five relevant records for inclusion. An additional five records were identified through the grey literature search. This included searching conferences and congresses of relevance, as well as trial registries. Therefore, the SLR ultimately included a total of 10 relevant publications, relating to five independent studies. The PRISMA for the overall SLR including number of studies included and excluded can be seen in Figure 62. The list of included and excluded studies can be found in Table 45 and Table 46.[36]

Figure 64. PRISMA diagram



Source: BMS data on file (2024)[36]

Of the 10 included publications, five publications reported on the KN-177 clinical trial (NCT02563002). KN-177 was a multicenter, international, open-label, phase III trial of PEMBRO versus chemotherapy in patients with previously untreated MSI-H and/or dMMR mCRC.[9,10,23,41,42] The study was conducted from February 11, 2016 to July 17, 2023 at 192 sites in 23 countries and involved a total of 307 patients.[9,10,23,41,42] Andre et al. (2020)[23] was considered the primary publication of KN-177 with subsequent ad-hoc studies reporting follow-up or subgroup data.

The five remaining publications identified were related to ongoing trials. CM 8HW (NCT04008030) trial is a phase 3, multinational study, conducted by BMS,[3,43] of relevance to this submission.

The remaining three studies identified, do not yet have results available and do not include relevant comparators and therefore are not relevant to this submission: the COMMIT trial (NCT02997228) is an ongoing phase 3, United States (US) based study of

atezolizumab,[44] NCT04258111 is a phase 2 study of IBI310 in Combination With sintilimab in China,[45] and NCT05652894 is a phase 3 study, of pucotenlimab in China.[46]

The primary objective of the CM 8HW trial is to compare the clinical benefit, as measured by PFS, objective response rate, and OS, achieved by NIVO in combination with IPI or by NIVO monotherapy in participants with MSI-H/dMMR mCRC.[3,43]

Study details of relevant included publications and trials can be found in Table 45.

Table 45. Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
KN-177 NCT02563002[9,10,23,41,42]	To assess the efficacy and safety of PEMBRO versus chemotherapy	RCT	Patients with dMMR/MSI-H mCRC.	PEMBRO 200 mg vs. Investigator's choice of chemotherapy	▪ PFS per RECIST v1.1 by BICR in the ITT population ▪ OS (the time from randomisation to death from any cause) ▪ Median follow-up at final analysis: 73.3 months	▪ ORR per RECIST v1.1 by central review ▪ Safety and tolerability in all treated participants
CM 8HW NCT04008030[3,43] (Ongoing)	To compare the clinical benefit achieved by NIVO in combination with IPI or by NIVO monotherapy versus chemotherapy.	RCT	Patients with dMMR/MSI-H mCRC.	NIVO mono, NIVO 240 mg + IPI vs. investigator's choice of FOLFOX or FOLFIRI, which could be combined with bevacizumab or cetuximab	▪ PFS by BICR in patients with dMMR/MSI-H status centrally confirmed ▪ Median follow-up: 31.51 months.	▪ PFS by BICR in patients with dMMR/MSI-H status locally confirmed ▪ PFS by investigator in patients with dMMR/MSI-H status centrally confirmed ▪ PFS by BICR in patients with dMMR/MSI-H status centrally confirmed

RCT = randomised control trial, dMMR = deficient in mismatch repair, MSI-H = high microsatellite instability, mCRC = metastatic colorectal cancer, PFS = progression-free survival, BICR = blinded independent central review, ITT = intention to treat.

Source: BMS data on file (2024)[36]

H.1.4 Excluded full-text references

Table 46 presents the publications that were excluded during the full-text screening along with the reason for exclusion.

Table 46. Overview of excluded full-text publications

First author, year	Title	Reason for exclusion
Chen, 2020	A Study of Efficacy and Safety of Fruquintinib (HMPL-013) in Participants With Metastatic Colorectal Cancer	Patient population
Sinicrope, 2015	Analysis of Molecular Markers by Anatomic Tumor Site in Stage III Colon Carcinomas from Adjuvant Chemotherapy Trial NCCTG N0147 (Alliance)	Patient population
Tikidzhieva, 2012	Microsatellite instability and Beta2-Microglobulin mutations as prognostic markers in colon cancer: results of the FOGT-4 trial	Patient population
Lenz, 2024	Modified FOLFOX6 plus bevacizumab with and without nivolumab for first-line treatment of metastatic colorectal cancer: Phase 2 results from the CheckMate 9X8 randomized clinical trial.	Patient population
Martinelli, 2021	Cetuximab Rechallenge Plus Avelumab in Pretreated Patients With RAS Wild-type Metastatic Colorectal Cancer The Phase 2 Single-Arm Clinical CAVE Trial.	Patient population
Arnold, 2024	FRESCO-2: A global phase 3 multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients (pts) with refractory metastatic colorectal cancer (mCRC).	Patient population
Morris, 2024	SWOG S2107: Randomized phase II trial of encorafenib and cetuximab with or without nivolumab for patients with previously treated, microsatellite stable, BRAFV600E metastatic and/or unresectable colorectal cancer.	Study design
Overman, 2024	Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study: A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/ bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC)-NRG-GI004/SWOG-S1610.	Study design
Satake, 2024	First report of the randomized phase III study of bi-weekly trifluridine/tipiracil (FTD/ TPI) plus bevacizumab (BEV) vs. FTD/TPI monotherapy for chemorefractory metastatic colorectal cancer (mCRC): JCOG2014 (ROBiTS).	Patient population
Lumish, 2022	PD-1 blockade alone for mismatch repair deficient (dMMR) locally-advanced rectal cancer.	Patient population

First author, year	Title	Reason for exclusion
Cohen, 2022	One-year duration of nivolumab plus ipilimumab in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI/dMMR) metastatic colorectal cancer (mCRC): Long-term follow-up of the GERCOR NIPICOL phase II study.	Patient population
André, 2023	KEYSTEP-008: phase II trial of pembrolizumab-based combination in MSI-H/dMMR metastatic colorectal cancer.	Study design
Dasari, 2023	Subgroup analyses of safety and efficacy by number and types of prior lines of treatment in FRESCO-2, a global phase III study of fruquintinib in patients with refractory metastatic colorectal cancer.	Patient population
Yoshino, 2023	LBA7 Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the KEYNOTE-177 study Asia subgroup.	Duplicate
Elez, 2023	SEAMARK: phase II study of first-line encorafenib and cetuximab plus pembrolizumab for MSI-H/dMMR BRAFV600E-mutant mCRC.	Study design
Kawazoe, 2023	Lenvatinib plus pembrolizumab versus standard of care for previously treated metastatic colorectal cancer (mCRC): the phase 3 LEAP-017 study.	Patient population
Kopetz, 2023	SEAMARK: Randomized phase 2 study of pembrolizumab + encorafenib + cetuximab vs pembrolizumab alone for first-line treatment of BRAF V600E-mutant microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC).	Study design
Hecht, 2023	STELLAR-303: A phase 3 study of XL092 in combination with atezolizumab versus regorafenib in patients with previously treated metastatic colorectal cancer (mCRC).	Patient population
Overman, 2023	NRG-GI004/SWOG-S1610: Colorectal Cancer Metastatic dMMR Immuno-Therapy (COMMIT) study-A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC).	Study design
Cercek, 2022	PD-1 Blockade in Mismatch Repair-Deficient, Locally-Advanced Rectal Cancer.	Patient population
Oh, 2022	Phase II study of durvalumab monotherapy in patients with previously treated microsatellite instability-high/mismatch repair-	Patient population

First author, year	Title	Reason for exclusion
	deficient or POLE-mutated metastatic or unresectable colorectal cancer.	
Hu, 2022	Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally-advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomized, phase 2 trial.	Patient population
Yoshino, 2022	46MO FRESCO-2: A global / multiregional phase III clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with metastatic colorectal cancer.	Patient population
Osterlund, 2022	Impact of gender on demographics, resectability, resections, systemic treatment, adverse events and outcomes in metastatic colorectal cancer (mCRC) patients (RAXO-study).	Study design
Lima, 2022	Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study: A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/ atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC)-NRG-GI004/SWOG-S1610.	Study design
Ciombor, 2022	EA2201: An ECOG-ACRIN phase II study of neoadjuvant nivolumab plus ipilimumab and short course radiation in MSI-H/dMMR rectal tumors.	Study design
André, 2022	P-27 Phase 2 study of pembrolizumab-based combination therapy in patients with microsatellite instability-high or mismatch repair-deficient stage IV colorectal cancer.	Study design
André, 2022	P-12 A phase 3 study of nivolumab (NIVO), NIVO+IPIlimumab (IPI), or chemotherapy for microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): CheckMate 8HW.	Outcomes
Morris, 2022	Phase I/II trial of encorafenib, cetuximab, and nivolumab in patients with microsatellite stable, BRAFV600E metastatic colorectal cancer.	Patient population
Lima, 2022	NRG-GI004/SWOG-S1610: Colorectal cancer metastatic dMMR immuno-therapy (COMMIT) study-A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC).	Study design
Kopetz, 2022	BREAKWATER: Randomized phase 3 study of encorafenib (enco) + cetuximab (cet) +/- chemotherapy for first-line treatment (tx) of	Study design

First author, year	Title	Reason for exclusion
	BRAF V600E-mutant (BRAFV600) metastatic colorectal cancer (mCRC).	
Baretti, 2021	A phase 2 trial of gemcitabine and docetaxel in patients with metastatic colorectal adenocarcinoma with methylated checkpoint with forkhead and ring finger domain promoter and/or microsatellite instability phenotype.	Patient population
Taieb, 2021	Avelumab versus standard second line treatment chemotherapy in metastatic colorectal cancer patients with microsatellite instability: The SAMCO-PRODIGE 54 randomized phase II trial.	Patient population
Stahler, 2020	Single-nucleotide variants, tumor mutational burden and microsatellite instability in patients with metastatic colorectal cancer: Next-generation sequencing results of the FIRE-3 trial.	Study design
Damato, 2020	Phase II study on first-line treatment of NIVolumab in combination with folfoxiri/bevacizumab in patients with Advanced COloRectal cancer RAS or BRAF mutated - NIVACOR trial (GOIRC-03-2018).	Patient population
Antoniotti, 2020	AtezoTRIBE: A randomized phase II study of FOLFOXIRI plus bevacizumab alone or in combination with atezolizumab as initial therapy for patients with unresectable metastatic colorectal cancer.	Study design
Chen, 2020	Effect of Combined Immune Checkpoint Inhibition vs Best Supportive Care Alone in Patients with Advanced Colorectal Cancer: The Canadian Cancer Trials Group CO.26 Study.	Patient population
Morse, 2019	Safety of Nivolumab plus Low-Dose Ipilimumab in Previously Treated Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer.	Patient population
Hara, 2018	Phase II KEYNOTE-164 study of pembrolizumab (pembro) monotherapy for patients (pts) with previously treated, mismatch repair-Deficient (dMMR) advanced colorectal cancer (CRC): Primary and Japan subgroup analyses.	Patient population
Goey, 2017	Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal cancer: Updated results and molecular subgroup analyses of the phase 3 CAIRO3 study.	Patient population
Okuma, 2023	Phase II Trial of Nivolumab in Metastatic Rare Cancer with dMMR or MSI-H and Relation with Immune Phenotypic Analysis (the ROCK Trial).	Patient population
Zhang, 2023	Pucotenlimab in patients with advanced mismatch repair-deficient or microsatellite instability-high solid tumors: A multicenter phase 2 study.	Patient population

First author, year	Title	Reason for exclusion
Justesen, 2023	Evaluating the efficacy and safety of neoadjuvant pembrolizumab in patients with stage I-III MMR-deficient colon cancer: a national, multicentre, prospective, single-arm, phase II study protocol.	Study design
Coutzac, 2022	Immunotherapy in MSI/dMMR tumors in the perioperative setting: The IMHOTEP trial.	Patient population
Li, 2021	Subcutaneous envafolimab monotherapy in patients with advanced defective mismatch repair/microsatellite instability high solid tumors.	Patient population
Chalabi, 2020	Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers.	Patient population
Klingbiel, 2015	Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial.	Patient population
André, 2015	Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study.	Patient population
Pectasides, 2015	Randomized phase III clinical trial comparing the combination of capecitabine and oxaliplatin (CAPOX) with the combination of 5-fluorouracil, leucovorin and oxaliplatin (modified FOLFOX6) as adjuvant therapy in patients with operated high-risk stage II or stage III colorectal cancer.	Patient population
Mekenkamp, 2012	Mucinous adenocarcinomas: poor prognosis in metastatic colorectal cancer.	Outcomes
Ogino, 2012	Predictive and prognostic roles of BRAF mutation in stage III colon cancer: results from intergroup trial CALGB 89803.	Patient population
Hutchins, 2011	Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer.	Patient population

Source: BMS data on file (2024)[36]

H.1.5 Quality assessment

Risk of bias was assessed using Cochrane ROB Tool (version 2). Andre et al. (2020)[23] was the primary publication for KN-177 and was rated as having an overall low ROB (Table 47). However, it should be noted that within the trial, efficacy data were analysed through intention to treat analyses, while safety data included the as-treated population. This means that participants were analysed according to the interventions they received, even if their assigned intervention group was different. The study provided no

information on any adjustment made to the data using prognostic factors that predict deviations from intended intervention.

Ongoing trials could not be evaluated as information required to conduct the ROB assessment was not available.

Table 47. Risk of bias assessment

Study	Domain 1: Risk of bias arising from the randomisation process	Domain 2: Risk of bias due to deviations from the intended interventions	Domain 2: Risk of bias due to deviations from the intended interventions	Domain 3: Risk of bias due to missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result
KN-177[23]	Low	Low	Some concerns - Safety data focused on as-treated population. Study provided no information on any adjustments made to the data using prognostic factors that predict deviations from intended intervention.	Low	Low	Low
CheckMate 8HW[1]	Low	Low	Some concerns - Safety data focused on all-treated population.	Low	Low	Low

H.1.6 Unpublished data

The unpublished data used in this submission are all sourced from the CM 8HW clinical trial and are based on the CSR.[1,12,47]

Appendix I. Literature searches for health-related quality of life

The utility data used in the cost-effectiveness model are based on the EQ-5D results from the CM 8HW trial; therefore, a literature search for HRQoL was not used.

Appendix J. Literature searches for input to the health economic model

To guide the modelling process, a targeted literature review (TLR) was conducted to identify published cost-effectiveness analyses in the untreated mCRC population. The search was conducted using the NICE database as there is significant transparency in their evidence-based recommendations.

Appendix K. Other therapeutic indications approved by EMA

Melanoma

OPDIVO as monotherapy or in combination with IPI is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Relative to NIVO monotherapy, an increase in progression-free survival and overall survival for the combination of NIVO with IPI is established only in patients with low tumour PD-L1 expression.

Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Non–small cell lung cancer (NSCLC)

OPDIVO in combination with IPI and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising epidermal growth factor receptor mutation or anaplastic lymphoma kinase translocation.

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC after prior chemotherapy in adults.

Neoadjuvant treatment of NSCLC

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable NSCLC at high risk of recurrence in adult patients **whose tumours have PD-L1 expression ≥ 1%.**

Malignant pleural mesothelioma (MPM)

OPDIVO in combination with IPI is indicated for the first-line treatment of adult patients with unresectable MPM.

Renal cell carcinoma (RCC)

OPDIVO as monotherapy is indicated for the treatment of advanced RCC after prior therapy in adults.

OPDIVO in combination with IPI is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced RCC.

OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced RCC.

Classical Hodgkin lymphoma (cHL)

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory cHL after autologous stem cell transplant and treatment with brentuximab vedotin.

Squamous cell cancer of the head and neck (SCCHN)

OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic SCCHN in adults progressing on or after platinum-based therapy.

Urothelial carcinoma

OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

Adjuvant treatment of urothelial carcinoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle-invasive urothelial carcinoma (MIUC) with tumour-cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC.

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

OPDIVO in combination with IPI is indicated for the treatment of adult patients with dMMR or MSI-H metastatic CRC after prior fluoropyrimidine-based combination chemotherapy.

Oesophageal squamous cell carcinoma (OSCC)

OPDIVO in combination with IPI is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic OSCC with tumour-cell PD-L1 expression ≥ 1%.

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic OSCC with tumour-cell PD-L1 expression ≥ 1%.

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Adjuvant treatment of oesophageal cancer (OC) or gastro-oesophageal junction cancer (GEJC)

OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with OC or GEJC who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with human epidermal growth factor receptor 2–negative advanced or metastatic gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score ≥ 5.

Appendix L. References for appendices

1. BMS data on file. Bristol Myers Squibb. Interim clinical study report for study CA2098HW. 2024.

2. BMS data on file. Bristol Myers Squibb. A phase 3 randomized clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. 2024.

3. Andre T, Elez E, Van Cutsem E, Jensen LH, Bennouna J, Mendez G, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): first results of the CheckMate 8HW study. J Clin Oncol. 2024;42(3_suppl):LBA768-LBA.

4. Lenz H-J, Lonardi S, Elez E, Van Cutsem E, Jensen LH, Bennouna J, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): expanded efficacy analysis from CheckMate 8HW. J Clin Oncol. 2024;42(16_suppl):3503.

5. Andre T, Lonardi S, Wong KYM, Lenz HJ, Gelsomino F, Aglietta M, et al. Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Ann Oncol. 2022 Oct;33(10):1052-60.

6. Lenz HJ, Van Cutsem E, Luisa Limon M, Wong KYM, Hendlisz A, Aglietta M, et al. First-line nivolumab plus low-dose ipilimumab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: the phase II CheckMate 142 study. J Clin Oncol. 2022 Jan 10;40(2):161-70.

7. Lenz H-J, Overman MJ, Van Cutsem E, Limon ML, Wong KYM, Hendlisz A, et al. First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 64-month (mo) follow-up from CheckMate 142. J Clin Oncol. 2024;42(3_suppl):97.

8. Overman MJ, Lenz H-J, Andre T, Aglietta M, Wong MK, Luppi G, et al. Nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): five-year follow-up from CheckMate 142. J Clin Oncol. 2022;40(16_suppl):3510.

9. Diaz LA, Jr., Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2022 May;23(5):659-70.

10. Shiu K, André T, Kim TW, Vittrup Jensen B, Jensen LH, Punt CJA, et al. Pembrolizumab versus chemotherapy in microsatellite instability–high/mismatch repair–deficient metastatic colorectal cancer: 5-year follow-up of the randomized phase III KEYNOTE-177 study. Ann Oncol. 2023;34:S1271-72.

11. Andre T, Amonkar M, Norquist JM, Shiu KK, Kim TW, Jensen BV, et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021 May;22(5):665-77.

12. BMS data on file. Bristol Myers Squibb. Interim clinical study report for study CA2098HW-section 14 tables. 2024.

13. Higgins J, Li T, Deeks J, (editors). Chapter 6. Choosing effect measures and computing estimates of effect. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions version 65 Cochrane, 2024; 2024. https://onlinelibrary.wiley.com/doi/10.1002/9781119536604.ch6.

14. BMS data on file. Bristol Myers Squibb. CA2098HW: Health-related quality of life analysis. Results for health-related quality of life analysis in patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer treated with nivolumab alone, nivolumab in combination with ipilimumab, or chemotherapy (CheckMate 8HW). November 2023 database lock. 5 June 2024.

15. Shiu K, André T, Kim TW, Vittrup Jensen B, Jensen LH, Punt CJA. Pembrolizumab versus chemotherapy in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) metastatic colorectal cancer (mCRC): 5-year follow-up of the randomized phase III KEYNOTE-177 study. Presented at European Society for Medical Oncology (ESMO); 20-24 October 2023.

16. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012 Feb 1;12:9.

17. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. 2016.

18. Burnham KP, Anderson DR. Multimodel inference - understanding AIC and BIC in model selection. Sociol Method Res. 2004 Nov;33(2):261-304.

19. Raftery AE. Bayesian model selection in social research. Sociol Methodol. 1995;25:111-63.

20. NICE. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2023. https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741. Accessed 11 April 2024.

21. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91.

22. Phillipo D. multinma: network meta-analysis. R Package Version 0.3.0 ed. 2020.

23. Andre T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med. 2020 Dec 3;383(23):2207-18.

24. BMS data on file. Bristol Myers Squibb. PFS forest plot from CheckMate 8HW locally confirmed population. 2024.

25. Goey KKH, Sørbye H, Glimelius B, Adams RA, André T, Arnold D, et al. Consensus statement on essential patient characteristics in systemic treatment trials for metastatic colorectal cancer: supported by the ARCAD Group. Eur J Cancer. 2018 Sep;100:35-45.

26. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part II: multivariate data analysis--an introduction to concepts and methods. Br J Cancer. 2003 Aug 4;89(3):431-6.

27. Akaike H. A new look at the statistical model identification. IEEE Trans Autom Control. 1974;19:716-23.

28. Zhao QY, Luo JC, Su Y, Zhang YJ, Tu GW, Luo Z. Propensity score matching with R: conventional methods and new features. Ann Transl Med. 2021 May;9(9):812.

29. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998 Oct 15;17(19):2265-81.

30. Statistics Denmark. HISB8: life table (2 years tables) by sex, age and life table. 2024. https://www.statbank.dk/HISB8. Accessed 23 October 2024.

31. Palmer S, Borget I, Friede T, Husereau D, Karnon J, Kearns B, et al. A Guide to selecting flexible survival models to inform economic evaluations of cancer immunotherapies. Value Health. 2023 Feb;26(2):185-92.

32. Latimer N. Decision Support Unit, ScHARR, University of Sheffield. NICE DSU Technical Support Document 14. Survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. 2013. https://www.sheffield.ac.uk/nice-dsu/tsds/survival-analysis. Accessed 27 November 2024.

33. Feng L, Wang R, Zhao Q, Wang J, Luo G, Xu C. Racial disparities in metastatic colorectal cancer outcomes revealed by tumor microbiome and transcriptome analysis with bevacizumab treatment. Front Pharmacol. 2023;14:1320028.

34. Tougeron D, Sueur B, Zaanan A, de la Fouchardiére C, Sefrioui D, Lecomte T, et al. Prognosis and chemosensitivity of deficient MMR phenotype in patients with metastatic colorectal cancer: an AGEO retrospective multicenter study. Int J Cancer. 2020 Jul 1;147(1):285-96.

35. BMS data on file. Bristol Myers Squibb. Analyses of health-related quality of life in patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer treated with nivolumab alone, nivolumab in combination with ipilimumab, or chemotherapy (CheckMate 8HW), utilities by health state analysis report (database lock: 15 November 2023). 2024.

36. BMS data on file. Bristol Myers Squibb. Comparative efficacy and safety of 1L therapies in patients with MSI H/dMMR metastatic colorectal cancer: systematic literature review. 2024.

37. Cumpston MS, McKenzie JE, Welch VA, Brennan SE. Strengthening systematic reviews in public health: guidance in the Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. J Public Health (Oxf). 2022 Dec 1;44(4):e588-e92.

38. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.

39. Koopman M, Kortman GA, Mekenkamp L, Ligtenberg MJ, Hoogerbrugge N, Antonini NF, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer. 2009 Jan 27;100(2):266-73.

40. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. In: Cochrane Handbook for Systematic Reviews of Interventions. 2019:205-28. https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119536604.ch8. Accessed 26 November 2024.

41. Yoshino T, Andre T, Kim TW, Yong WP, Shiu KK, Jensen BV, et al. Pembrolizumab in Asian patients with microsatellite-instability-high/mismatch-repair-deficient colorectal cancer. Cancer Sci. 2023 Mar;114(3):1026-36.

42. Yoshino T, André T, Shiu K-K, Kim TW, Jensen BV, Jensen LH, et al. O7-3 Pembrolizumab vs chemotherapy in MSI-H / dMMR metastatic colorectal cancer: KEYNOTE-177 final analysis Asia subgroup. Ann Oncol. 2022;33:S471.

43. ClinicalTrials.gov NCT04008030. A study of nivolumab, nivolumab plus ipilimumab, or investigator's choice chemotherapy for the treatment of participants with deficient mismatch repair (dMMR)/microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC) (CheckMate 8HW). 5 August 2024. https://clinicaltrials.gov/study/NCT04008030. Accessed 2 September 2024.

44. ClinicalTrials.gov NCT02997228. Combination chemotherapy, bevacizumab, and/or atezolizumab in treating patients with deficient DNA mismatch repair metastatic colorectal cancer, the COMMIT Study. 29 August 2024. https://clinicaltrials.gov/study/NCT02997228. Accessed 2 September 2024.

45. ClinicalTrials.gov NCT04258111. IBI310 in combination with sintilimab in patients with DNA mismatch repair deficient (dMMR)/microsatellite instability high (MSI-H) locally-advanced or metastatic colorectal cancer. 19 September 2022. https://clinicaltrials.gov/study/NCT04258111. Accessed 2 September 2024.

46. ClinicalTrials.gov NCT05652894. A study of HX008 compared to chemotherapy in the first-line treatment of subjects with MSI-H/dMMR metastatic colorectal cancer. 15 December 2022. https://clinicaltrials.gov/study/NCT05652894. Accessed 2 September 2024.

47. BMS data on file. Bristol Myers Squibb. Interim clinical study report for study CA2098HW-section 14 figures. 2024.

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