Single Technology Appraisal

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

Contents:

The following documents are made available to consultees and commentators:

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

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

Document B

Company evidence submission

October 2020

File name	Version	Contains confidential information	Date
		Yes	

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Abbreviations

AE	Adverse event
AIC	Akaike Information Criteria
BIC	Bayesian Information Criteria
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CG	Clinical guidance
CI	Confidence interval
CIN	Chromosomal instability
CMS1	Consensus molecular subtype 1
CR	Complete response
CRC	Colorectal cancer
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
dMMR	DNA mismatch repair deficient
DOR	Duration of response
DSU	Decision Support Unit
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EGFR	anti- epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ C-30	European Organization for Research and Treatment of Cancer QLQ-C-30
EQ-5D	EuroQol 5-dimensions
FOLFIRI	folinic acid, 5-fluorouracil, irinotecan
FOLFOX	folinic acid, 5-fluorouracil, oxaliplatin
GI	Gastrointestinal
HrQoL	Health related Quality of Life
HTA	Health Technology Appraisal
ICER	Incremental Cost Effectiveness Ratio
IRRC	Independent radiology review committee
ITC	Indirect treatment comparison
LYG	Life Years Gained
MAIC	Matching-adjusted indirect comparison
mCRC	Metastatic colorectal cancer
MMR	DNA mismatch repair

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MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSI-L	Microsatellite instability low
MSS	Microsatellite stable
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NR	Not reached
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PCR	Polymerase chain reaction
PD	Relapsed or progressed disease
PFS	Progression-free survival
PICOS	Population-Intervention-Comparators-Outcomes-Study
PSA	Probabalistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
pMMR	DNA mismatch repair proficient
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	Relapse-free survival
SAE's	Serious Adverse Events
SD	Stable disease
SLR	Systematic literature review
STC	Simulated treatment cohort
TA	Technology Assessment
TTR	Time to recurrence
VAS	Visual analogue scale
VEGF	anti-vascular endothelial growth factor
WTP	Willingness-to-pay

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication (███ ███). The technology is nivolumab in combination with ipilimumab (hereafter referred to as NIVO+IPI), approved for use in other indications. The decision problem that this submission addresses is presented in Table 1.

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Table 1.The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with previously treated recurrent or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.	███████████████████████ ███████████████████████████ ████ ████████████████████████████	The wording has been updated to reflect the proposed marketing authorisation, in line with the NICE reference case.
Intervention	Nivolumab with ipilimumab.	Nivolumab with ipilimumab.	NA
Comparator(s)	For people having second- or subsequent-line treatment: • Single-agent irinotecan (after FOLFOX) • FOLFIRI (after either FOLFOX or CAPOX) • FOLFOX (after either FOLFIRI or CAPOX) • Raltitrexed (if 5-fluorouracil and folinic acid are not suitable) • Trifluridine-tipiracil • Best supportive care (BSC)	For people having second- or subsequent-line treatment: • Trifluridine-tipiracil • FOLFOX • FOLFIRI • BSC. Note: given the limited use of raltitrexed and single-agent irinotecan in UK clinical practice, we do not believe these comparisons should inform decision making. However, cost-effectiveness assessments versus these comparators has been provided for completeness with the final scope.	Following clinical validation[1], the key comparators in a previously treated MSI-H mCRC population were highlighted as being: • FOLFOX/FOLFIRI (both used interchangeably, primarily in 2L. Estimated 40% patients each). • Trifluridine-tipiracil (mainly used in 3L and beyond, once other options are exhausted, including clinical trial enrolment). Estimated 5–10% of patients. • BSC (mainly used in later lines). Usually the last treatment option for patients who cannot tolerate active treatment. Estimated 6% of patients. Clinical expert opinion confirmed that both single agent irinotecan and

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			raltitrexed are rarely used in clinical practice (<5% patients combined), and mainly in patients where other treatments are contraindicated.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	As per the scope, with the following specifics: • progression-free survival *(BICR-assessed, investigator-assessed)* • response rates *(investigator-assessed ORR, BICR-assessed ORR, duration of response).*	Efficacy outcomes have been presented to be in line with those reported in the CM142 study.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent	Adhering to the reference case: • the cost-effectiveness is expressed in terms of an incremental cost per quality-adjusted life year (QALY). • A lifetime horizon is used. • the economic analyses has been conducted from an NHS and Personal Social Services perspective. • the Patient Access Scheme (PAS) has been applied in economic analyses for all BMS products. The economic modelling does not include costs associated with diagnostic testing for microsatellite instability status in people with metastatic colorectal cancer who would not otherwise have been tested.	As noted in the final scope, current NICE guidance recommends that all people with colorectal cancer should be offered testing when first diagnosed, using immunohistochemistry for mismatch repair proteins or MSI testing to identify tumours with dMMR.[2, 3] This was based on economic evaluations conducted as part of Diagnostics Guidance 27 [DG27].[3] Further, NG151 notes that testing for dMMR may inform systemic therapy choices for those with non-metastatic colorectal cancer, but the NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer already

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	treatment technologies will be taken into account. The economic modelling should include the costs associated with diagnostic testing for microsatellite instability status in people with metastatic colorectal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.		recommends such testing for all people with colorectal cancer when first diagnosed.[4] For this reason no further recommendations were made about testing for deficient DNA mismatch repair.

This assumption is validated by clinical experts, who note that this is an easy test to carry out and that all patients should be tested given it is in the NICE guidance. In particular, given that immuno-oncology therapies are available for this group, testing for this MSI high status is even more important.[1]

Further, this is in line with ERG comments on an ongoing mCRC appraisal (ID1598), where it was noted that testing for *BRAF* status is "recommended in the updated NICE guideline (NG151) for all patients with mCRC at first diagnosis to help guiding the selection of systemic anti-cancer therapy. Consequently, the test is becoming a standard care and does not present an incremental cost |

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			compared with comparators for the use of the technology."[4] In summary, as per NICE guidance, all patients should now be tested across the UK.[3] Therefore, we believe that the appropriate economic analysis for this STA should be that of NIVO+IPI itself, excluding diagnostic test costs.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	No equality issues have been identified or are anticipated.	NA
BICR: blinded independent central review; BSC: best supportive care; CAPOX: capecitabine plus oxaliplatin; DNA: deoxyribonucleic acid; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan; FOLFOX: 5 fluorouracil, folinic acid, and oxaliplatin; NA: not applicable; NICE: National Institute for Health and Care Excellence; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year.			

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B.1.2   Description of the technology being appraised

A description of the technology being appraised in this submission (NIVO+IPI), is presented in Table 2. The draft summary of product characteristics (SmPC) for Nivolumab (Opdivo®) and for Ipilimumab (Yervoy®) are presented in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Nivolumab plus ipilimumab (Opdivo® + Yervoy®)

Mechanism of action	CTLA-4 and PD-1 are immune checkpoints involved in T-cell differentiation and function:
	
	 • PD-1 is specifically involved in inhibiting T-cell destruction of healthy 'self-cells' at the effector (later) stage of the immune response.
	
	     o Tumour cells can exploit this pathway by up-regulating proteins that engage PD-1 to limit the activity of T-cells at the tumour site.
	
	 • CTLA-4 is specifically involved in inhibiting constant T-cell production to avoid 'self-damage' in the priming and activation (early) stage of the immune response.
	
	     o This pathway 'switches off' the immune response to tumour antigens, stopping production of activated T-cells in human malignancy.
	
	 Nivolumab and ipilimumab are both fully human, monoclonal immunoglobulin antibodies (IgG4 and IgG1k HuMAb, respectively) that act as checkpoint inhibitors of PD-1 and CTLA-4, respectively, at their distinct yet complementary positions within the T-cell response pathway:
	
	 • Nivolumab stops the inactivation of T-cells at the tumour site, allowing the active T-cells to infiltrate and destroy the tumour.
	
	 • Ipilimumab stops the immune response from being 'switched off', thus allowing the production of active T-cells to continue and increasing the number of activated T-cells surrounding the tumour.
	
	 NIVO+IPI therefore potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" cell); this results in destruction of the tumour through pre-existing, intrinsic processes.

Marketing authorisation/CE mark status	A regulatory submission was made to the EMA on the ▇▇▇▇▇▇▇. The earliest point at which an opinion from CHMP could be anticipated would be ▇▇▇▇▇ with a corresponding regulatory approval available in ▇▇▇▇▇.
Indications and any restriction(s) as described in the summary of	▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ ▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇▇ ▇▇

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product characteristics (SmPC)	████████████████████████████████████The combination of NIVO+IPI has been granted an EMA marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults, and for previously untreated advanced renal cell carcinoma that is considered to be at moderate or high risk of worsening. Nivolumab monotherapy is licensed for the following indications: • Advanced (unresectable or metastatic) melanoma in adults, and in patients following who have had surgery for the removal of melanoma that has spread to the lymph nodes or elsewhere in the body. • Non-small cell lung cancer in patients previously treated with chemotherapy. • Advanced renal cell carcinoma in previously treated patients. • Classical Hodgkin lymphoma after an autologous stem cell transplant and treatment with brentuximab vedotin. • Metastatic squamous cell cancer of the head and neck following platinum-based therapy. • Advanced (unresectable or metastatic) urothelial cancer following platinum-based therapy. Ipilimumab monotherapy is licensed for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older.
Method of administration and dosage	Intravenous infusion. Nivolumab 3mg/kg IV with ipilimumab 1mg/kg IV every 3 weeks for 4 doses followed by nivolumab 240mg IV.
Additional tests or investigations	As detailed in the SmPC, NIVO+IPI treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Hospital oncology units already have the staffing and infrastructure needed for the administration of IV oncology therapies. Patients eligible to receive NIVO+IPI have mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) mCRC. Current NICE guidance recommends that all people with colorectal cancer should be offered testing when first diagnosed, using immunohistochemistry to detect DNA mismatch repair proteins or PCR to detect microsatellite instability[5], based on economic evaluations conducted as part of Diagnostics Guidance 27 [DG27][3]. Therefore, all patients will already be offered testing to identify dMMR/MSI status. It should be noted that this early testing will also inform other treatment choices.

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List price and average cost of a course of treatment	List price: Nivolumab: £2633.00 per 240mg vial; £1,097.00 per 100mg vial; £439.00 per 40mg vial. Ipilimumab: £15,000.00 per 200mg vial; £3,750 per 50mg vial. Average cost of a course of NIVO+IPI treatment is: Cycle 1-4: £10,503.68 Cycle 5+: £2,874.06 Patient Access Scheme (PAS) price: Nivolumab: ▆▆▆▆ per 240mg vial Ipilimumab: ▆▆▆▆ per 2 x 50mg vial Average cost of a course of NIVO+IPI treatment is: Cycle 1-4: ▆▆▆▆ Cycle 5+: ▆▆▆▆
Patient access scheme (if applicable)	There is a confidential simple discount PAS for nivolumab and for ipilimumab which applies to all current and future indications.
CTLA-4: cytotoxic T-lymphocyte antigen-4; dMMR: DNA mismatch repair; HuMAb: human monoclonal antibody; IgG: immunoglobulin; IPI: ipilimumab; IV: intravenous; mCRC: metastatic colorectal cancer; MSI-H: microsatellite instability-high; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NIVO: nivolumab; PAS: Patient Access Scheme; PCR: polymerase chain reaction; PD-1: programmed death-1; SmPC: Summary of Product Characteristics.	

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

B.1.3.1. Disease Background

Colorectal cancer (CRC) is a significant health problem. It is the third most prevalent cancer worldwide,[6] and the fourth most common cancer in the UK, accounting for 11.4% of all new cancer registrations in England in 2017.[7] Patients with metastatic CRC (mCRC) have a very poor prognosis with very few treatment options available once refractory to standard therapies or upon relapse.

CRC is the fourth most common cancer in the UK and the second biggest cancer killer, accounting for 10% of all cancer deaths in 2017.[8] Survival from CRC is highly dependent on cancer stage at diagnosis, where 5-year survival in England can be higher than 90% for those diagnosed at localised stage, but around only 10% for those diagnosed at the metastatic stages (Table 3).[9] The survival statistics for patients in England on current standard therapies highlight the need for more efficacious treatments. As identified by the systematic literature review (SLR) described in Section B.2.1.1 and Appendix D, in previously treated mCRC patients survival is particularly reduced, as demonstrated by the systematic literature review described in Section B.2.9.1, where the weighted mean of reported median OS value was 9.48 months for comparators overall (range: 6.05 months to 12.73 months). UK clinical experts note that outcomes in mCRC patients with MSI-H/dMMR status are likely poorer, noting that this may be related to a higher proportion of patients with *BRAF* mutation and Lynch syndrome. This is supported by much of the published clinical evidence, as described in Section B.1.3.2.1.

Table 3. Colorectal cancer survival in England (age 15–99, diagnosed between 2013 and 2017)[9]

Stage at diagnosis	Number of patients	One-year age-standardised survival (%)	Five-year age-standardised survival (%)
All stages	166,013	78.3	58.4
Stage 1	25,988	97.8	91.7
Stage 2	38,521	94.1	84.1
Stage 3	44,098	89.2	64.9
Stage 4 (metastatic)	38,697	43.9	10.3
Unknown	18,560	62.9	41.6

CRC is a heterogeneous disease that develops slowly over a number of years and the vast majority (more than 90%) of CRC cases are adenocarcinomas.[10] Development of an adenocarcinoma occurs slowly, through multiple stages (termed the 'adenoma-carcinoma

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sequence') over years, even decades, which start with benign, pre-malignant, or malignant polyps occurring on the epithelial lining of the colon or rectum.[11] Around 20% of CRC cases have a family history, with some genetic syndromes (e.g. Lynch syndrome) carrying an increased risk of CRC. However, the majority of CRC cases are linked to environmental factors, such as diet, lifestyle and environmental and food-borne mutagens.[11]

The symptomatic burden of CRC is high. Symptoms of CRC include (in isolation or in combination) a persistent change in bowel habit such as higher frequency, looser stools or abdominal pain; blood in the stools not caused by haemorrhoids; abdominal pain; discomfort or bloating after eating; a mass in the abdomen; a feeling of needing to strain when defecating; weight loss; and anaemia.[12, 13] In severe cases, patients may suffer from bowel obstruction. Symptoms of bowel obstruction include intermittent or occasionally severe abdominal pain caused by eating; unintentional weight loss with persistent abdominal pain; a painful swelling of the abdomen; an inability to pass stool; and vomiting.[13] Early signs of CRC can be subtle, hence around a quarter of CRC cases have metastases at the time of diagnosis (stage 4; mCRC),[14] with only 10% of these expected to be alive at 5 years.[15]

B.1.3.2. The dMMR/MSI-H subtype

The majority of CRCs develop via the chromosomal instability (CIN) pathway, whereas a small proportion (12–15%) arise from the microsatellite instability (MSI) pathway due to defects in the DNA mismatch repair (MMR) system.[16-18] Tumours that develop as a consequence of this defective MMR pathway are classified as 'deficient MMR' (dMMR) or 'MSI-high' (MSI-H),[19] and can develop sporadically, or from an inherited germline mutation in a MMR gene (e.g. Lynch Syndrome). Sporadic dMMR tumours carry somatic mutations in the *BRAF* oncogene in approximately half of cases,[17] which may affect prognosis: dMMR *BRAF* (−) patients have demonstrated significantly improved overall survival compared to dMMR *BRAF* (+) patients,[20] a finding corroborated by UK clinicians.[1] MSI-H/dMMR CRC is less common in metastatic tumours (4%) than in early tumour stages.[21-23] Patients with metastatic MSI-H/dMMR mCRC have very short survival outcomes, few treatment options and significant unmet medical need.

B.1.3.2.1. Impact of MSI-H/dMMR status on mCRC outcomes

The impact of MSI status on prognosis is not fully understood. Emerging evidence suggests disease stage may be a factor in prognosis, with patients in the later (metastatic) stage who are dMMR/MSI-H likely showing worse prognosis.[16] However, very few studies have assessed the impact of MSI status on survival in mCRC, and no evidence has been identified that has assessed the impact of MSI-H/dMMR status on previously treated mCRC patients.[24]

Early stage CRC

A systematic review[25] and meta-analysis[26] of available data across all stages of CRC found an association between MSI and favourable prognosis in terms of overall survival (OS) and disease-free survival at early stages of the disease only. A study by Benatti et al (2005) identified that MSI-H was a prognostic factor for improved survival in CRC patients, but that

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this benefit was not statistically significant in stage I or stage IV CRC.[27] Similarly, dMMR patients with stage II and III colon cancers showed a significant improvement in OS, disease-free survival and time to recurrence compared with patients with proficient DNA mismatch repair (pMMR) tumours.[28] By contrast, another study by Merok et al (2013) identified similar 5-year OS rates between MSI and MSS tumours (69% and 61% respectively), but 5-year relapse-free survival was higher in MSI patients (67.1% versus 54.7%), and the beneficial impact was relevant to stage II CRC but not stage III CRC.[29] In support of this, Hutchins et al (2011) observed lower recurrence in CRC patients with dMMR than in patients with pMMR; however, this study predominantly enrolled patients with stage II CRC.[30] It is also worth noting that the positive prognostic impact of MSI-H status may be limited to patients without disease recurrence; Kim et al (2016) identified that patients with stage I-III CRC with MSI-H had improved disease-free survival compared with patients with MSI-L/MSS, but following recurrence OS was significantly worse (five-year survival from recurrence: 15.6% versus 47.9%).[31]

MSI-H is also associated with a poorer response to 5-fluorouracil (5-FU) chemotherapy, and there appears to be no survival benefit for 5-FU adjuvant chemotherapy in early stage CRC patients who are MSI-H.[32-34] A recent study in colon cancer patients showed that more patients with dMMR had disease progression following neoadjuvant chemotherapy than patients with pMMR.[35]

<u>Metastatic CRC</u>

Evidence suggests that patients with dMMR/MSI-H CRC benefit less from conventional chemotherapy and have a shorter OS than patients with pMMR once the disease is at the metastatic stage. [22, 23, 31, 36-42] A meta-analysis conducted by Des Guetz et al in 2009 concluded that there was no significant improvement associated with MSI-H status in terms of response rate.[43] However, this was based on evidence derived from first-line mCRC patients and included response rate only.[44-49] Of the six studies included within the meta-analysis, two described improved survival in MSI-H patients,[48, 49] one described worse survival outcomes,[44] and one described no difference, although this may have been due to low patient numbers.[46] Since this meta-analysis was conducted, evidence has been mixed; while some studies have concluded that there is no difference in outcomes between MSI-H and MSS patients,[21, 50] several large-scale studies suggest that survival is impaired in metastatic patients with dMMR/MSI-H status.[22, 23, 31, 36-42, 51-54] Further, ██ ██ ██████████████████████████████████████.[55] UK clinical experts assert that patients with MSI-H mCRC experience worse outcomes than those in the overall mCRC population, particularly following initial relapse.[1] Evidence to describe outcomes in patients with MSI-H mCRC is summarised in Table 4.

Additionally, *BRAF* may be more frequently mutated in patients with sporadic MSI-H mCRC (*BRAF* V600E),[21, 23, 39, 50, 56] and this is prognostic of poor outcomes in this patient population.[23]

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This is validated by UK clinical experts, who stated that around one third of UK MSI-H/dMMR mCRC patients have *BRAF* mutations and suggest that this mutation may be associated with the poor outcomes in this patient population. One study which identified lower progression-free survival (PFS) and OS in patients with dMMR mCRC suggested that this could be attributed to *BRAF* mutation status.[23] In support of this conclusion, two recent large scale studies evaluating first-line mCRC therapies identified worse survival outcomes (median PFS and median OS) for patients with consensus molecular subtype 1 (CMS1; MSI immune), which is characterised by MSI, CIMP, hypermethylation and *BRAF* mutation.[37, 57-59]

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Table 4. Metastatic CRC studies

Author	Year	Study design	Disease stage	Number of prior therapies	MSI-H or dMMR	Impact of MSI-H/dMMR	Number of patients	Comments
Brueckl WM, Moesch C, Brabletz T, et al.[48]	2003	Prospective	NR	0	MSI-H	MSI -H CRC might have a better response and survival than MSS CRC in palliative first-line treatment.	MSS (n=36) MSI-H (n=7)	RR: MSI-H - 72%, MSS - 41% median survival: MSI-H 33 months, MSS - 19 months
Cohen R, Hain E, Cervera P, et al.[56]	2017	Retrospective	Metastatic	NR	dMMR	Worse prognosis of patients with sporadic dMMR than Lynch syndrome--related dMMR or overall population	129 patients, of which 48 had sporadic dMMR and 81 had Lynch syndrome	Median OS from stage IV diagnosis: 43.9 months for the overall population 23 months for SP Not reached for LS Median PFS with first-line chemotherapy for pts with unresectable metastasis (n = 61); 3.9 months for SP 5.0 months for LS
Des Guetz G, Mariani P, Cucherouss et J, et al.[45]	2007	Prospective	Metastatic	0	MSI-H	No difference in ORR or OS in MSI-H and MSS patients	MSI-H (n=9) and MSS (n=31)	PFS: MSI-H - 8.6 months, MSS - 8.3 months OS: MSI-H - 16 months, MSS - 22.5 months
Des Guetz G, Uzzan B, Nicolas P, et al.[43]	2009	Review	Metastatic	NR	MSI-H	No benefit of chemotherapy in terms of the response rate for MSI-H compared with MSS	MSI-H (N=91) MSS (N=873)	Review includes Muller 2008,[46] Des Guetz 2007,[45] Fallik 2003,[47] Brueckl 2003, [48] Liang 2002,[49] Koopman 2007.[44]

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Author	Year	Study design	Disease stage	Number of prior therapies	MSI-H or dMMR	Impact of MSI-H/dMMR	Number of patients	Comments
Fallik D, Borrini F, Boige V, et al.[47]	2003	Retrospective	Metastatic	1	MSI-H	MSI-H showed a better response to chemotherapy than MSS	MSI-H (N=7) MSS (N=65)	MSI-H: Responders - 4 Non-responders - 3 MSS: Responders - 7 Non-responders - 58
Fujiyoshi K, Yamamoto G, Takenoya T, et al.[21]	2017	Prospective	Stage IV	NR	MSI-H	No significant survival difference between MSI-H and MSS CRC stage IV patients	MSI-H (N=15) MSS (N=386)	Survival: MSS - 2.5 years, MSI-H - 3.92
Gelsomino F, Barbolini M, Spallanzani A, et al.[24]	2016	Review	Stages I-IV	NR	MSI-H	No benefit of chemotherapy in terms of response rate for MSI-H compared with MSS tumours	NR	Cites Des Guetz 2009[43]
Goldstein J, Tran B, Ensor J, et al.[50]	2014	Retrospective	Metastatic	0	MSI-H	Patients with MSI-H mCRC do not appear to have improved outcomes.	55 all MSI-H	Median OS- 11.5 months from the start of chemo
Innocenti F, Ou F-S, Zemla T, et al.[36]	2017	Randomized phase III trial	Metastatic	0	MSI-H	OS does not differ between MSI-H and MSI-S pts	MSI-H (N=21), MSS (N=320)	OS in Bevacizumab arm: MSI-H - 30 months, MSS - 32.6 months OS in cetuximab arm: MSI-H - 11.2 months, MSS - 30.1 months

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Author	Year	Study design	Disease stage	Number of prior therapies	MSI-H or dMMR	Impact of MSI-H/dMMR	Number of patients	Comments
Koopman M, Kortman GA, Mekenkamp L, et al.[22]	2009	Randomised phase III study	Advanced	0	dMMR	dMMR resulted in worse OS and PFS and a decreased disease control rate than pMMR	pMMR (N=453) dMMR (N=16)	Patients were randomised between first-line capecitabine, second-line irinotecan and third-line capecitabine + oxaliplatin (sequential treatment arm) vs first-line capecitabine + irinotecan, and second-line capecitabine/oxaliplatin (combination treatment arm). Median OS: pMMR - 17.9 months, dMMR - 10.2 months Median PFS: pMMR - 6.9 months, dMMR - 4 months Disease control rate: pMMR- 83%, dMMR - 56%

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Author	Year	Study design	Disease stage	Number of prior therapies	MSI-H or dMMR	Impact of MSI-H/dMMR	Number of patients	Comments
Koopman M, Kortman GA, Mekenkamp L, et al.[44]	2007	Randomised trial	Advanced	0	MSI-H	Disease control and OS was lower in MSI	MSI - 512	In 461 evaluable pts, disease control (CR+PR+SD=4 months) in 12 pts with MSI was 58% [95% CI 28%-85%] and in 449 without MSI 83% [95% CI 79%-86%, p= 0.03].The median OS in pts with MSI was 7 months [95% CI 4–17] and in pts without MSI 18 months [95% CI 16–19, log rank p=0.08].
Lenz H-J, Ou F-S, Venook AP, et al.[37]	2017	Randomized phase III trial	Metastatic	0	CMS1	Patients with CMS1 had lower OS and PFS	CMS1 (N=55) CMS2 (N=183) CMS3 (N=114)	OS (months): CMS1 - 17 CMS2 - 39.7 CMS3 - 23.7 PFS (months): CMS1 - 6.5 CMS2 - 13.3 CMS3 - 9.6
Liang JT, Huang KC, Lai HS, et al.[49]	2002	Non-randomised controlled	Stage IV	NR	MSI-H	These findings implied that among patients with HDFL therapy the MSI-H group had better survival than the MSI-S– group. However, in patients without HDFL therapy, the prognosis was similarly poor regardless of MSI-H status.	MSI-H HDFL+ (N=35) MSS HDFL+ (N=134) MSI-H HDFL- (N=17) MSS HDFL- (N=58)	ORR: MSI-H 65.71%, MSS - 35.07% Median survival: MSI-H HDFL+ - 24 months, MSS HDFL - 13 months, MSI-H HDFL- - 7 months, MSS HDFL- - 7 months

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Author	Year	Study design	Disease stage	Number of prior therapies	MSI-H or dMMR	Impact of MSI-H/dMMR	Number of patients	Comments
Muller CI, Schulmann K, Reinacher-Schick A, et al.[46]	2008	prospective randomised phase III	Metastatic	0	MSI-H	Lower rate of disease control in MSI-H. No correlation between MSI-H and OS/PFS	MSI-H (n=4), non MSI-H (n=100)	PFS: MSI-H - 2.5 months, Non-MSI-H - 7.9 months OS: MSI-H - NR, Non-MSI-H - 18.9 months Disease control: MSI-H - 2 patients, Non-MSI-H - 86 patients PD: MSI-H - 2 patients, Non-MSI-H - 4 patients
Nopel-Dunnebacke S, Schulmann K, Reinacher-Schick A, et al.[41]	2014	Retrospective	Metastatic	0	MSI-H	MSI-H tumours tend to have lower disease control rates when treated with an oxaliplatin/fluoropyrimidine combination	Overall 229	DCR for MSI-H tumours 65%, P53 overexpression 85%
Nordholm-Carstensen A, Krarup PM, Morton D, et al.[42]	2015	Prospective cohort study	Metastatic	NR	dMMR	dMMR had no impact on survival	pMMR (N=5709) dMMR (N=983)	NR
Smith CG, Fisher D, Claes B, et al.[39]	2013	Prospective	Metastatic or locally advanced	0	MSI-H	MSI-H was associated with worse survival.	NR	Evidence reported in Kaplan-Meier plots
CMS: consensus molecular subtype; CR: complete response; CRC: colorectal cancer; DFS: disease-free survival; HDFL: high-dose 5-FU plus leucovorin; dMMR: DNA mismatch repair deficient; LS: Lynch syndrome; MSI: microsatellite instability; MSI-H: microsatellite instability high; MSS: microsatellite stable; NR: not reached; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; pMMR: DNA mismatch repair proficient; PR: partial response; SP: sporadic; TTR: time to recurrence.								

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B.1.3.2.2. MSI-H/dMMR testing

In 2017, NICE recommended molecular testing for all patients when first diagnosed with CRC using immunohistochemistry for mismatch repair proteins or MSI testing to identify tumours with dMMR.[3] This was based on economic evaluations conducted as part of Diagnostics Guidance 27 [DG27].[3] Further, NG151 notes that testing for dMMR may inform systemic therapy choices for those with non-metastatic colorectal cancer, but the NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer already recommends such testing for all people with colorectal cancer when first diagnosed.[4] For this reason no further recommendations were made about testing for deficient DNA mismatch repair.

Clinical experts consulted during this appraisal highlight that guidelines recommend MSI-H testing and acknowledged that this should be routinely available at diagnosis.[3, 4] Some advisors commented on possible variation across the UK, predicting about 25% of centres may not conduct this testing routinely. However, advisors noted that this is an easy test to conduct, and one of the few tests that is in NICE guidance, thus the expectation should be that 100% of centres conduct these tests, particularly once there are effective therapies available for these patients (immuno-oncology therapies).[1]

B.1.3.3. Clinical pathway of care

Treatment for mCRC aims to prolong survival, improve quality of life and/or make the primary tumour or metastases suitable for resection. The National Institute for Health and Care Excellence (NICE) has undertaken several Technology Appraisals assessing therapies for the treatment of mCRC, but there is no specific guidance on treatment options for patients with dMMR/MSI-H mCRC (with these patients following generic mCRC guidance).

For the small group of dMMR/MSI-H mCRC patients treatment options are very limited and primarily based on evidence obtained from the overall mCRC population. Hence, based on the current clinical pathway, the majority of MSI-H/dMMR mCRC patients will be treated with the limited number of treatments currently available for the overall mCRC population.

The diagnosis and management of CRC is described in NICE clinical guideline 151 (published, 29 January 2020),[4] as well as the NICE pathways describing management of CRC,[5] and mCRC.[60] The current clinical treatment pathway for mCRC, is shown in Figure 1. This pathway is the same regardless of MSI status.

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Figure 1. Current NICE clinical pathway for metastatic colorectal cancer in NHS England[60]

Capecitabine is recommended as first-line treatment of metastatic colorectal cancer (the guidance recommendations originally included tegafur with uracil, but this is no longer available)

Flourouracil chemotherapy is recommended as first-line treatment of metastatic colorectal cancer. The My5-FU assay is only recommended for use in research for guiding dose adjustment in people having flurouracil chemotherapy by continuous infusion

(The guidance recommendations originally included
-FOLFOX as first-line treatment then single-agent irinotecan as second-line treatment or FOLFIRI as second-line treatment XELOX as first-line treatment then FOLFIRI as second-line treatment
-Raltitrexed for patients with advanced colorectal cancer who are intolerant to 5-FU and folinic acid, or for whom these drugs are not suitable (e.g. patients that develop cardiotoxicity)
but this is no longer available)

Interim treatment regimens during the COVID-19 pandemic

Test for mutations if suitable for systemic anti-cancer treatment

Incurable metastatic disease with an asymptomatic primary tumour

Considerations for specific metastases
- Bone metastases
- Liver metastases
- Lung metastases
- Peritoneal metastases

First-line chemotherapy

First-line biological therapy

Subsequent or alternative therapy

Supportive and palliative care

Cetuximab in combination with FOLFOX or FOLFIRI for previously untreated EGFR-expressing, RAS wild-type metastatic colorectal cancer

Panitumumab in combination with FOLFOX or FOLFIRI for previously untreated RAS wild-type metastatic colorectal cancer

Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended

Bevacizumab in combination with 5-FU plus folinic acid, with or without irinotecan is not recommended

Trifluridine–tipiracil is recommended, within its marketing authorisation, provided certain criteria are met

Best supportive care

Regorafenib for metastatic colorectal cancer was terminated as no evidence submission was received

In the first line setting, oral therapy with capecitabine is recommended as an option for the first-line treatment of metastatic colorectal cancer, with the choice of regimen (5-FU/FA or capecitabine) to be made jointly by the individual and the clinician(s) responsible for treatment.[60]

For patients in the previously treated setting, the NICE recommended treatments for mCRC are trifluridine-tipiracil[60] or best supportive care (BSC), following treatment with currently available therapies.

Combination chemotherapy leads to adverse events (any grade [AE]) or intolerance in approximately 95% of patients, with more than half the patients experiencing grade 3-5 AEs. Some patients are left with life-altering consequences, such as persistent sensory neuropathy. Overall survival is modestly improved with trifluridine-tipiracil compared to placebo (7.1 months versus 5.3 months), however response rates are very low (1.6%), survival benefit is limited to weeks, and more than half the patients experience grade 3-5 AEs. Additionally, 53% of patients had a delay of 4 days or more in beginning their next cycle owing to toxicity.[61] Treatments for metastatic disease (FOLFOX/FOLFIRI/raltitrexed) were omitted from the new guidance (NG151),[4] therefore the recommendations around their use in mCRC remains unclear.

Furthermore, treatment options do not take into account MSI status. The MSI-H CRC molecular subtype has a distinctly different pathological manifestation including poor differentiation, accumulation of lymphocytes, and intertumoral heterogeneity.[62] Thus, MSI

cancers will not necessarily have the same response to the chemotherapeutic strategies used to treat MSS tumours. Indeed, patients with MSI-H status have consistently demonstrated poorer responses to chemotherapy treatment regimens than patients with MSI-L/MSS status, [32-34, 63] particularly those with metastatic disease.[46, 64]

To understand the current management of MSI-high mCRC in UK clinical practice, 5 UK clinical experts were consulted.[1] These were the learnings:

- In the UK, 5-fluorouracil/folinic acid (5-FU/FA) and irinotecan (FOLFIRI), 5-FU/FA and oxaliplatin (FOLFOX) or oxaliplatin and capecitabine (XELOX) are the primary treatments used in the first-line metastatic setting (alone or in combination with anti-EGFR agents)

- In second line, the predominant treatment options are; FOLFIRI (used in patients who have received FOLFOX or XELOX in first line), or FOLFOX (used in patients who have received FOLFIRI in the first-line setting).

- Treatment options for the small proportion of patients surviving beyond second line in the metastatic setting include trifluridine-tipiracil or best supportive care (BSC), though these options are known to have low efficacy.

- Raltitrexed and single agent irinotecan are very rarely used (1-2% of population).

According to these UK clinical advisors, treatments for CRC have not advanced in many years, hence they seek access to immunotherapies (including nivolumab and ipilimumab) through compassionate use schemes or clinical trial enrolment, highlighting a substantial unmet need for a therapy with proven efficacy and a favourable safety profile in the management of MSI-H mCRC. UK clinical opinion is that NIVO+IPI is a treatment that works for these patients and is completely different to current standard of care. Advisors reported positive experiences with nivolumab in combination with ipilimumab, and nivolumab monotherapy, through the individual patient request scheme and the Covid interim fund.[1]

In the current treatment pathway for MSI-H mCRC, the predominant regimens used in the second-line setting represent the same modality as those used in the first-line setting. Given the high toxicity of existing chemotherapy-based treatment options, there is a significant unmet need for therapies with proven efficacy and a favourable safety profile. NIVO+IPI represents a new immunotherapy treatment modality that addresses the immune dysfunction and is anticipated to provide durable benefit for MSI-H mCRC patients.

B.1.3.4. Proposed treatment

The proposed treatment regimen in this submission is combination therapy with NIVO+IPI for ██ ██ In 2018, NIVO+IPI was granted accelerated approval by the FDA for MSI-H or dMMR mCRC that has progressed

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following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan,[65] after demonstrating efficacy benefit in Checkmate 142, results of which are presented in this submission. The FDA also granted the NIVO+IPI combination Breakthrough Therapy Designation for this potential indication in 2018, designed to expedite the development and review of drugs that are intended to treat a serious condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).[66] A recent retrospective real-word study of 49 previously treated patients with dMMR mCRC from 13 UK sites treated with nivolumab alone or NIVO+IPI demonstrated significant clinical benefit and acceptable toxicities (described in Section B.2.13.4.1).[67] A currently active Phase III randomised controlled trial (CheckMate 8HW)[68] (not included in this submission) will provide further efficacy and safety evidence to supplement CheckMate 142.

Neither nivolumab nor ipilimumab currently has EMA marketing authorisation for previously treated dMMR/MSI-H mCRC.

Nivolumab and ipilimumab are both fully human, monoclonal immunoglobulin antibodies (IgG1k and IgG4 HuMAb, respectively) that act as checkpoint inhibitors of PD-1 and CTLA-4 at their distinct, yet complementary, positions within the T-cell response pathway[69] (Figure 2):

1. Nivolumab stops the inactivation of T-cells at the tumour site, allowing the active T-cells to infiltrate and destroy the tumour

2. Ipilimumab stops the immune response from being 'switched off' which allows the production of active T-cells to continue, increasing the number of activated T-cells surrounding the tumour.

Clinical development of nivolumab as an oncologic agent is ongoing and the program is broad and extensive. Nivolumab is approved for the treatment of several types of cancer in multiple regions including the US (Dec-2014), the EU (Jun-2015), and Japan (Jul-2014). There are numerous clinical studies evaluating the efficacy and safety of nivolumab as a single agent and in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies across multiple tumour types, and lines of therapy.

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Figure 2. Rationale for combining nivolumab and ipilimumab therapies[69]
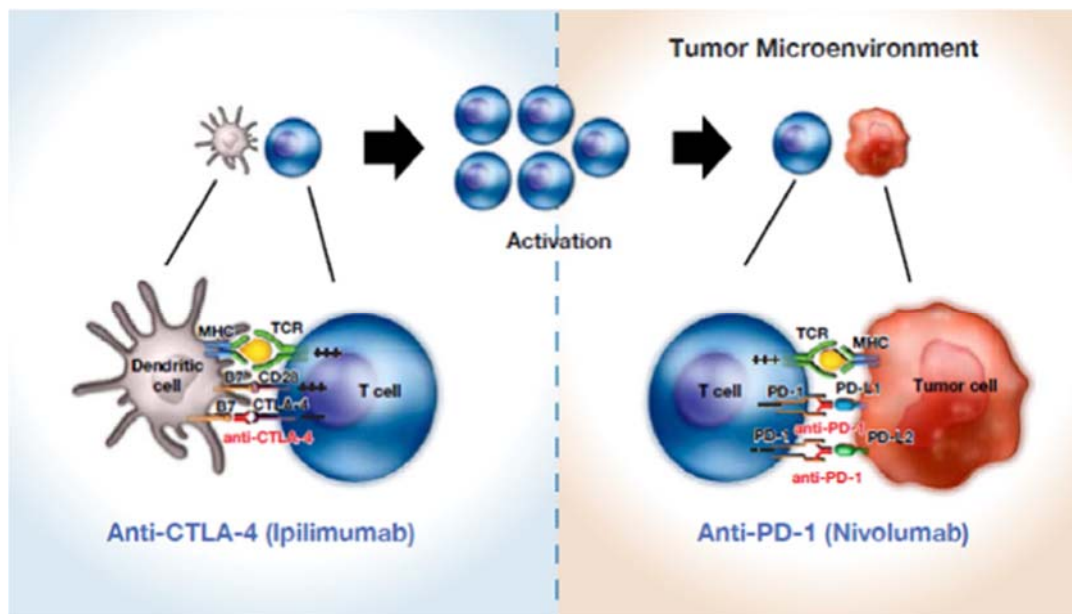
Abbreviations: CTLA-4: cytotoxic T-lymphocyte antigen 4; MHC: major histocompatibility complex; PD-1: programmed death-1; TCR: T-cell receptor.

The regimen potentiates immune-mediated tumour destruction; stimulating the patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes. The combination of CTLA-4 and PD-1 blockers has a synergistic effect on activation of an anti-tumour immune response, and can increase response rates and survival rates of the patients.[70]

Blockade of CTLA-4, which is primarily involved in regulation of T-cell activation in lymph nodes/tissues and in suppression of dendritic cell activity via Treg cells, acts synergistically with blockade of PD-1 that is mainly involved in inhibition of effector T-cell and NK cell activation in peripheral tissues, and in induction of Treg cell differentiation (Figure 3).[70] Studies have shown that MSI-H tumours are particularly sensitive to immune checkpoint blockade.[71, 72] CRC with DNA dMMR/MSI-H positive tumours is expected to respond to immunotherapy due to high levels of tumour neoantigens, tumour-infiltrating lymphocytes and expression of immune checkpoints.[70]

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Figure 3. Synergistic effects of PD-1 & CTLA-4 blockade[70]
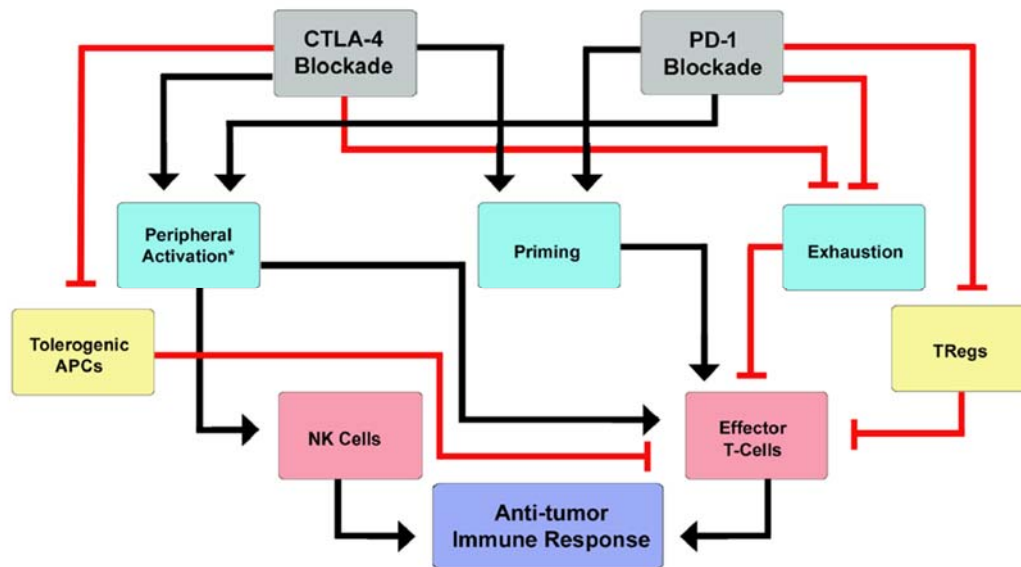
*NK cells do not express CTLA-4 and are not expected to be activated by CTLA-4 blockade.

Abbreviations: APC: antigen-presenting cell; CTLA-4: cytotoxic T-lymphocyte antigen 4; NK: natural killer; PD-1: programmed death-1; TRegs: regulatory T-cells.

NIVO+IPI represents a new immunotherapy treatment modality, with different toxicity profile and, if recommended by NICE, would be the first immunotherapeutic treatment option for previously treated mCRC patients, providing an alternative to retreatment with standard chemotherapy options.

Despite the various treatment options for mCRC, the benefit of these therapies remains modest beyond first line and toxicity is observed in almost all patients, thus highlighting the unmet medical need for more effective therapies. Taking together its mechanism of action and clinical data, NIVO+IPI is anticipated to provide significant durable clinical benefit for these patients, addressing the unmet need that exists in the current standard of care.

Nivolumab is currently approved as OPDIVO® in the European Union (EU), for specific types of melanoma (including in combination with ipilimumab), NSCLC, RCC (including in combination with ipilimumab), squamous cell cancer of the head and neck (SCCHN), classical Hodgkin lymphoma (cHL) and urothelial carcinoma (UC).[73] Clinical development of nivolumab remains actively ongoing in a broad and extensive programme. Development and registration planning continue in expanded patient populations in the currently indicated tumours as well as other solid tumours and haematologic malignancies.

Ipilimumab is currently approved as YERVOY® in the EU for the treatment of unresectable or metastatic melanoma (including in combination with nivolumab), and for treatment of RCC (in combination with nivolumab).[74]

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The combination of nivolumab and ipilimumab at different dose ratios has been approved for use in multiple indications globally. Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg has been approved for use in 1L RCC in the EU, US, Australia, Switzerland, Japan, and Canada, as well as in MSI-H CRC in the US. Additionally, nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg has been approved for use in advanced melanoma in the EU, US, and several other countries including Australia, Switzerland and Japan.

B.1.4 Equality considerations

No equality issues have been identified or are anticipated

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B.2. Clinical effectiveness

Key points

- Previously treated patients with dMMR/MSI-H mCRC have a poor prognosis and receive treatments based on highly limited evidence.

- NIVO+IPI is the first treatment available in the EU with proven effectiveness for treatment-experienced dMMR/MSI-H mCRC patients, addressing the significant unmet need in this small patient population.

- NIVO+IPI therapy has significant benefits in terms of patient-relevant outcomes, including high response rates and improved survival (both PFS and OS) versus current treatment alternatives.

- As of the February 2019 cut-off, median OS was ██████████ but OS at one year was 84.9% and at two years was ███, indicating a significantly longer OS than for comparators.

- Similarly, median PFS was ██ months, with one-year PFS of 71.6% and two-year PFS of ███, which exceeds that observed for comparators.

- Based on available evidence, the safety profile of NIVO+IPI can be considered manageable in the context of alternative therapies. Further, this safety profile is well-established based on that observed in other indications.

- Mean OS for NIVO+IPI is predicted to be ███ months while mean PFS is predicted to be ██ months. In the unadjusted ITC, mean OS was 7.22–17.32 months for comparators and mean PFS was 1.83–6.79 months. Applying MAIC methodology, comparator mean OS ranged from 7.13 months to 17.06 months, while mean PFS ranged from 1.81 months to 6.92 months.

- NIVO+IPI meets the end-of-life criteria for this small patient group that would be eligible for treatment under the proposed indication.

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of metastatic colorectal cancer.

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B.2.1.1. Systematic literature review

Databases were searched from database inception to June 2020. In total, the SLR identified 366 publications, including 194 unique studies. Further details on how many studies informed each comparator can be found in the SLR report (Appendix D) and in Section B.2.9.1.

Table 5. Studies identified in the clinical effectiveness SLR

	Total Publications	Total Unique Studies	Total Unique Studies (RCTs)	Total Unique Studies (non-RCTs)
2020 SLR	366	194	66	128
RCT: randomised controlled trial; SLR: systematic literature review.				

B.2.2. List of relevant clinical effectiveness evidence

Evidence to describe the effectiveness of NIVO+IPI for the treatment of dMMR/MSI-H mCRC is primarily derived from CheckMate 142,[75] a Phase II open-label, multi-centre, non-randomised, 2-stage Simon design trial of nivolumab monotherapy, NIVO+IPI, or an investigator's choice chemotherapy to estimate the response rate in MSI-H CRC and non-MSI-H CRC.

The NIVO monotherapy, the non-MSI safety cohort, and further experimental cohorts in CheckMate 142 (NIVO plus cobimetinib; NIVO plus anti-LAG-3 antibody; and NIVO plus daratumumab) <u>will not be described in this submission</u>. The focus of this submission will be on the cohort of patients with recurrent or metastatic CRC that received combination treatment with NIVO+IPI.

The estimated study completion date is July 6, 2022.[75]

Supportive evidence is available from real-world evidence for NIVO+IPI, described in Section B.2.13.4.1.

B.2.2.1. Rationale for design of CheckMate 142

Although CRC is a relatively common cancer, incidence of dMMR/MSI-H or dMMR CRC is significantly lower (around 15% of early stage cases and around 4% of metastatic cases, regardless of treatment line).[7, 16-18, 21-23] Based on methods of calculating patient numbers outlined in previous mCRC HTAs this would equate to around 282 eligible patients in England with dMMR/MSI-H mCRC who have received previous therapy.[2] Because of this low prevalence, clinical trial recruitment of previously treated MSI-H or dMMR mCRC patients is severely limited.

Within this patient population, median overall survival (OS) remains short even with initiating first-line chemotherapy (median: 13.6 months),[23] so it can be expected that only a small

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proportion of this patient population would survive to receive later line therapies, limiting patient numbers to below that estimated for the overall mCRC population.[23] Taking this into account, a single-arm study was deemed ethical and relevant to facilitate a rapid assessment and confirmation of clinical activity in the dMMR/MSI-H mCRC population.

Therefore, given the large degree of unmet medical need for safe and effective ≥ 2L therapies in mCRC overall, including in patients with MSI-H/dMMR mCRC, with small patient numbers, a non-comparative study design for CheckMate 142 can be considered appropriate.

Table 6. Overview of clinical evidence: CheckMate 142

Study	CheckMate 142 (CA209-142)				
Study design	Ongoing Phase II, non-comparative, open-label, multi-centre trial.				
Population	Patients with metastatic or recurrent CRC with dMMR/MSI-H, at least 18 years old, with an ECOG performance status of 0 or 1 and measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1).[76, 77]				
Intervention(s)	NIVO+IPI combination therapy Other cohorts within CheckMate 142 assessed the safety and efficacy of NIVO as monotherapy and with other agents as combination therapy, but <u>these are not relevant to the indication under consideration.</u>				
Comparator(s)	Non-comparative study				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	Only available source of evidence describing the efficacy of NIVO+IPI for ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮▮▮▮▮▮▮. The base case analysis will apply data from the cohort of patients who are relevant to the indication under consideration only.				

Reported outcomes specified in the decision problem	• Overall survival
	• Progression-free survival (PFS)
	   ○ Investigator-assessed PFS
	   ○ BICR-assessed PFS
	• Response rates:
	   ○ Investigator-assessed objective response rate (ORR)
	   ○ BICR-assessed ORR
	• Adverse effects of treatment
	• Health-related quality of life (HRQoL)				

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| All other reported outcomes | Pharmacokinetic data was also collected. |

1L: first-line; BICR: blinded independent central review; CRC: colorectal cancer; dMMR: deficient mismatch repair; ECOG: Eastern Cooperative Oncology Group; HRQoL: health-related quality of life; IPI: ipilimumab; mCRC: metastatic colorectal cancer; MSI-H: microsatellite instability high; NIVO: nivolumab; ORR: objective response rate; RECIST: Response Evaluation Criteria in Solid Tumours

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

A summary of methodology for CheckMate 142 is provided in Table 7.

Table 7. Summary of methodology: CheckMate 142

Trial acronym	CheckMate 142
Trial design	Ongoing Phase 2, non-comparative, open-label, multi-centre trial.
Eligibility criteria for participants	Adults (≥18 years), with histologically confirmed metastatic or recurrent CRC or mCRC, assessed as dMMR and/or MSI-H, and disease progression following (or intolerance of) ≥1L treatment(s), which must include at least (i) a fluoropyrimidine, and (ii) oxaliplatin or irinotecan. Patients who refused chemotherapy for the treatment of metastatic or locally advanced disease were also eligible. Eligibility included ECOG performance status of 0 or 1 and measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1).[76, 77]
Settings and locations where the data were collected	Patients in the relevant cohort (the NIVO+IPI cohort) were treated at 28 sites in 8 countries.
Intervention	NIVO 3 mg/kg (60-minute intravenous [IV] infusion) plus IPI 1 mg/kg (90-minute IV infusion) once every 3 weeks for four doses and then NIVO 3 mg/kg IV once every 2 weeks until disease progression, discontinuation because of toxicity, death, withdrawal of consent, or study end (N=119).
Comparator	Non-comparative study.
Permitted and disallowed Concomitant medications	Permitted medications: 1) Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). 2) Adrenal replacement steroid doses including doses >10 mg daily prednisone. 3) A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen). 4) Supportive care for disease-related symptoms to all patients on the trial.

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Trial acronym	CheckMate 142
	Disallowed medications: 1) Palliative radiotherapy was not recommended while receiving study drugs, given the potential for overlapping toxicities with radiotherapy and nivolumab in combination with ipilimumab (if palliative radiotherapy was required, then study drugs were withheld for at least 1 week before, during, and 1 week after radiation). 2) Immunosuppressive agents (except to treat a drug-related adverse event). 3) Systemic corticosteroids >10 mg daily prednisone equivalent (except as stated under *Permitted medications*, or to treat a drug-related adverse event). 4) Live/attenuated vaccines (e.g., varicella, zoster, yellow fever, rotavirus, oral polio and MMR). 5) Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy described in *Permitted medications* or standard or investigational agents for treatment of cancer). Concomitant medications were collected within 14 days prior to first dose and through the study treatment period
Primary outcome	Investigator-assessed ORR.
Other outcomes used in the economic model/specified in the scope	ORR based on BICR determination Overall survival Progression-free survival Adverse effects of treatment Patient-reported outcomes (EORTC QLQ-C30 & EQ-5D questionnaires) completed before first dose and every 6 weeks thereafter.
Pre-planned subgroups	The BICR-assessed ORR using RECIST 1.1 was compared across the following baseline subgroups: • Age • Region • Gender • Race • Lynch syndrome • KRAS/BRAF mutation status • Baseline ECOG PS • Time from initial diagnosis to first dose • Primary tumour location • Number of prior systemic regimens received • time from completion of most recent prior therapy regimen to treatment • time from progression of most recent prior therapy regimen to treatment Key post-hoc subgroups are described in Section B2.7.
BICR: blinded independent central review; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ C30: European Organization for Research and Treatment of Cancer Quality of Life	

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Trial acronym	CheckMate 142

Questionnaire-Core 30; EQ-5D: Euroqol 5-dimensions; HRQoL health-related quality of life; IPI: ipilimumab; IV: intravenous; MMR: measles, mumps and rubella; NIVO: nivolumab; ORR: objective response rate; PS: performance status.

B.2.3.1. Study design

CheckMate 142 (NCT02060188) is an ongoing Phase II, open-label, non-randomised trial initiated by Bristol-Myers Squibb in March 2014 to examine if nivolumab monotherapy or combination therapy demonstrate a meaningful objective response rate (ORR > 30%) in patients with recurrent and metastatic colon cancer.[75, 78]

The combination of NIVO+IPI was chosen as an experimental arm due to the strong rationale that the anti–programmed death 1 (PD-1) antibody nivolumab, with its mechanism of action that abrogates immune tolerance, in combination with ipilimumab, an anti–cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) antibody that acts to up-regulate antitumour immunity, will have enhanced clinical activity in MSI-H/dMMR CRC. The combination of nivolumab and ipilimumab is more effective than either agent in monotherapy in the treatment of a variety of tumours including melanoma, lung, and renal cell carcinoma.[79-81]

Treatment arms included:

- nivolumab alone (mStage)

- **nivolumab in combination with ipilimumab in previously treated MSI-H patients (cStage) – Note: this forms the basis for the current HTA submission**

- nivolumab in combination with ipilimumab in previously untreated MSI-H patients (Cohort C3)

- nivolumab in combination with ipilimumab and cobimetinib for previously treated non-MSI-H patients (Cohort C4)

- nivolumab in combination with an anti-LAG3 agent for previously treated MSI-H patients (BMS-986016; Cohort C5)

- or nivolumab in combination with daratumumab for previously treated non-MSI-H patients (Cohort C6)

The combination of nivolumab and ipilimumab (cStage) was chosen as an experimental arm because of preclinical and preliminary clinical evidence suggesting synergy between nivolumab and ipilimumab. Available clinical data with nivolumab 3 mg/kg in combination with ipilimumab at 1 mg/kg has demonstrated incremental benefit relative to nivolumab 3 mg/kg monotherapy across multiple tumour types including MSI-H/dMMR mCRC.

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The multi-centre study comprises of study locations in North America (USA and Canada), Australia and Europe (Ireland, Belgium, Italy, France and Spain).[75] At the time the study was being set up it was not possible to include UK sites due to a paucity of testing availability, revealed during the feasibility process.

MMR/MSI status was detected by an accredited laboratory as per local regulations (IHC or PCR) and the procedure manual was the criteria to enrol patients. For PCR, individual testing sites were allowed to utilise a slightly different panel of markers incorporating alternative mononucleotide and/or dinucleotide markers. Regardless of the panel of markers, samples with instability in 30% or more of these markers were defined as MSI-H, whereas those with < 30% unstable markers were designated as MSI-low (MSI-L); samples with no detectable alterations were MSS. For IHC, there were four antibody markers to determine protein expression from the four MMR genes in the panel. Samples with loss of protein expression in one or more genes were defined as dMMR; those with intact protein expression in all four genes were defined as pMMR. Samples were subsequently centrally tested by PCR.[78]

As stated above, CheckMate 142 included cohorts who received nivolumab monotherapy or other nivolumab combination therapies, which are outside the scope of the proposed indication. As such, results are only presented for the cohort relevant to the proposed indication: the NIVO+IPI (cStage) of the CheckMate 142 study. Enrolment for this study was staggered (schematic is shown in Figure 4).[78, 82]

Figure 4. CheckMate 142: Study schematic and enrolment for cStage cohort

FPFV: first patient's first visit; LPFV: last patient's first visit; q2w: every 2 weeks; q3w: every 3 weeks.

B.2.3.2. Eligibility criteria

The key inclusion criteria for cStage of CheckMate 142 were as listed below; full inclusion criteria for all cohorts are available from the clinical study protocol:[78]

- Histologically confirmed CRC that is metastatic or recurrent

- Adults ≥18 years of age with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1

- MSI-H detected by an accredited laboratory per local regulations

- Prior treatment: progression during, after, or have been intolerant to ≥1 line treatment(s) for their metastatic disease, which must include at least:

  o A fluoropyrimidine, and oxaliplatin or irinotecan (patients who received oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of adjuvant therapy in order for oxaliplatin to count as a prior therapy needed for entry).

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OR

- Patients may have actively refused chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. The patient's refusal must have been thoroughly documented. The investigator discussed each individual patient refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

- Patients must have measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria for response assessment. Patients with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enrol provided the lesion(s) have demonstrated clear progression and can be measured accurately

- Patient was willing to comply to provide tumour tissue (archival or fresh biopsy specimen), including possible pre-treatment biopsy, for PD-L1 expression analysis and other biomarker correlative studies

- ECOG Performance Status of 0 or 1.[78]

B.2.3.3. Study medications

All patients who met eligibility criteria and were enrolled into the NIVO+IPI arm received NIVO 3mg/kg (60-minute intravenous [IV] infusion) and IPI 1 mg/kg (90-minute IV infusion) once every 3 weeks for four doses and then nivolumab 240mg IV once every 2 weeks until disease progression, discontinuation due to toxicity, death, withdrawal of consent, or study end (Figure 5). Dose modifications were not permitted. Dose interruptions for treatment related adverse events (TRAEs) were allowed.

Figure 5. CheckMate 142: Nivolumab plus ipilimumab dosing schedule

IPI: ipilimumab; NIVO: nivolumab

NIVO and IPI dosing calculations were based on the patient's body weight, and dose reductions and escalations were not permitted. Dose delays were permitted of <6 weeks for all drug-related AEs according to pre-specified criteria. Treatment was permanently discontinued according to pre-specified criteria, due to AE or disease progression.[83]

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B.2.3.4. Study endpoints

B.2.3.4.1 Primary endpoint

The primary objective of CheckMate 142 was to evaluate the investigator-assessed ORR in the MSI-H cohort, defined as the number of MSI-H patients with a best overall response of confirmed CR or PR, according to (RECIST) version 1.1 criteria, divided by the number of treated MSI-H patients. The best overall response was defined as the best response designation recorded between the date of first dose and the date of progression or the date of subsequent therapy, whichever occurred first. The investigator-assessed ORR was further characterised by the duration of response (DOR) and rate of CR.

Secondary and exploratory objectives of CheckMate 142 were as follows[78]:

- To evaluate ORR, as assessed by independent radiology review committee (IRRC), which was further categorised by DOR.

- To estimate PFS, defined as the time from first dosing date to the date of the first documented progression, as determined by the investigator, or death due to any cause, whichever occurred first.

- To estimate OS, defined as the time from first dosing date to the date of death.

- To determine the safety and tolerability of nivolumab monotherapy. Adverse events (AEs) and laboratory values were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

- To evaluate patient-reported health outcomes, including EQ-5D-3L (including EQ-VAS) and EORTC QLQ C-30.

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

B.2.4.1. Statistical analyses

Efficacy analyses were performed for the treated population, defined as all patients who received at least one dose of study medication within a given cohort.[78]

The primary endpoint (investigator-assessed ORR) was summarised using a response rate estimate and corresponding two-sided 95% exact CI. The method proposed by Atkinson and Brown[84] was used to estimate the CI, as this CI takes into account the group sequential nature of the two-stage Simon design. ORR was further characterised by the DOR and rate of CR. DOR was summarised for confirmed MSI-H subjects who achieve confirmed PR or CR using the Kaplan-Meier product-limit method. Median values of DOR, along with two-sided 95% CI

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(based on the log-log transformation), was calculated. An estimate of CR rate and corresponding two-sided 95% exact CI was provided using Clopper-Pearson method.[78]

ORR based on IRRC assessment was summarised in a similar method to the investigator-assessed ORR, and was also characterised by IRRC-assessed DOR and IRRC-assessed CR rate.[78]

PFS and OS was summarised descriptively for the MSI-H cohort using the KM product-limit method. Median values of PFS and OS, along with two-sided 95% CI (based on the log-log transformation), was calculated.[78]

When assessing OS, a patient who had not died was censored at their last known date alive. Similarly, when assessing PFS, patients who did not progress or died were censored on the date of their last evaluable assessment. Patients who did not have any on study tumour imaging assessments and did not die were censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable assessment prior to initiation of the subsequent anti-cancer therapy.[78]

B.2.4.2. Sample size and power calculation

Methods and results are only presented for the cohort relevant to the proposed indication (nivolumab as combination therapy for the treatment of patients with dMMR or MSI-H mCRC following prior therapy).

For the MSI-H cohort, a Simon optimal two-stage design was used to test the null hypothesis that the true ORR is ≤ 30% (not considered clinically compelling) with treatment. In the first stage, 19 patients were treated with nivolumab monotherapy. If there were 2 or fewer responses in these first 19 treated patients, the protocol would have been closed to further enrolment. If there were more than 2 but less than 7 responses in the first 19 treated patients, accrual to the monotherapy arm was stopped and the combination arm was opened for accrual.[78]

When accrual to the combination arm was opened to the MSI-H cohort as specified above, stage I of the Simon two-stage design was initiated in the combination arm with 19 treated patients (cStage 1). If there were 6 or fewer responses in these first 19 treated patients, accrual to the combination arm would have been stopped. Otherwise, approximately 29 additional patients were accrued to the combination arm (cStage 2) to target a total of 48 patients treated with combination therapy. Patients whose repeat testing did not confirm MSI-H status were replaced in order to obtain the required number of patients in each stage of the Simon design.[78]

The null hypothesis was to be rejected if 20 or more responses were observed in 48 treated patients in the treatment arm. Within a given treatment arm, this design yields a one-sided type I error rate of 5% and power of 90% when the true response rate is 52%.[78]

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B.2.5. Quality assessment of the relevant clinical effectiveness evidence

As previously described, no relevant randomised controlled trials evaluating NIVO+IPI combination therapy for the treatment of dMMR/MSI-H mCRC following prior therapy were identified, so evidence is derived from the non-comparative study, CheckMate 142 (NCT02060188).

As this study was not a randomised controlled trial, an assessment of the methodological quality was conducted based on the ROBINS-I tool for assessing risk of bias in non-randomised studies of interventions,[85] as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[86]

Table 8. Quality assessment of CheckMate 142[83]

Bias domain	Signalling question	Response
1. Bias due to confounding		
1.1	Is there potential for confounding of the effect of intervention in this study?	Y
1.2	Was the analysis based on splitting participants' follow up time according to intervention received?	NA
1.3	Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Y
1.4	Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y
1.5	**If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Y
1.6	Did the authors control for any postintervention variables that could have been affected by the intervention?	Y (ORR/PFS)/ N (OS)
1.7	Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Y
1.8	**If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Y
Risk of bias judgment		Moderate
2. Bias in selection of participants into the study		
2.1	Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	N
2.2	**If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?	NA

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Bias domain	Signalling question	Response
2.3	**If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	NA
2.4	Do start of follow-up and start of intervention coincide for most participants?	Y
2.5	**If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	NA
Risk of bias judgement		Low
3. Bias in classification of interventions		
3.1	Were intervention groups clearly defined?	Y
3.2	Was the information used to define intervention groups recorded at the start of the intervention?	Y
3.3	Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	N
Risk of bias judgement		Low
4. Bias due to deviations from intended interventions		
4.1	Were there deviations from the intended intervention beyond what would be expected in usual practice?	N
4.2	**If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	NA
Risk of bias judgement		Low
5. Bias due to missing data		
5.1	Were outcome data available for all, or nearly all, participants?	Y
5.2	Were participants excluded due to missing data on intervention status?	N
5.3	Were participants excluded due to missing data on other variables needed for the analysis?	N
5.4	**If N/PN to 5.1 or Y/PY to 5.2 or 5.N3**: Are the proportion of participants and reasons for missing data similar across interventions?	NA
5.5	**If N/PN to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?	NA
Risk of bias judgement		Low
6. Bias in measurement of outcomes		
6.1	Could the outcome measure have been influenced by knowledge of the intervention received?	N
6.2	Were outcome assessors aware of the intervention received by study participants?	Y

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Bias domain	Signalling question	Response
6.3	Were the methods of outcome assessment comparable across intervention groups?	NA
6.4	Were any systematic errors in measurement of the outcome related to intervention received?	N
Risk of bias judgement		Low
7. Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1	…. multiple outcome *measurements* within the outcome domain?	N
7.2	…. multiple *analyses* of the intervention-outcome relationship?	N
	….different *subgroups*?	N
Risk of bias judgement		Low

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. CheckMate 142

B.2.6.1.1 Baseline demographics

The majority of patients in CheckMate 142 were <65 years of age (68.1%) at baseline and median age was 58 years, as shown in Table 9. As per the inclusion criteria, all patients had ECOG status 0-1 and metastatic disease. All patients were disease stage IV at study entry. ███ ███████████. The majority of patients had received two or more prior lines or regimens of systemic cancer therapy. The most frequent prior systemic cancer therapies among all treated patients were 5-FU (99.2%), oxaliplatin (93.3%), bevacizumab or other VEGF-inhibitors (57.1%), and irinotecan (73.1%). 68.9% of patients were heavily pre-treated, having received prior 5FU-Oxa-Iri. Less than one fifth of patients (17%) had received prior radiation. The time from completion of most recent prior therapy regimen to start of treatment was <3 months for ██████ NIVO+IPI treated patients.[82, 83, 87]

Table 9. Baseline characteristics CheckMate 142[82, 83, 87]

		NIVO+IPI
Number of patients		119
Median age, years (range)		58 (21–88)
Age, years, n (%)	<65	81 (68.1)
	≥65	38 (31.9)
Gender, n (%)	Male	70 (58.8)
Race, n (%)	White	110 (92.4)

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	Black or African American	2 (1.7)
	Asian	3 (2.5)
	American Indian or Alaska Natives	1 (0.8)
	Other	3 (2.5)
ECOG*, n (%)	0	54 (45.4)
	1	65 (54.6)
Disease stage at initial diagnosis**, n (%)	II	14 (11.8)
	III	52 (43.7)
	IV	53 (44.5)
Primary tumour location, n (%)	Right colon	65 (54.6)
	Left and sigmoid colon	30 (25.2)
	Transverse colon	15 (12.6)
	Rectum	6 (5.0)
	Colon, NOS	3 (2.5)
Number of prior systematic regimens received, n (%)	0***	1 (0,8)
	1	27 (22.7)
	2	43 (36.1)
	≥3	48 (40.4)
Prior regimens received, n (%)	5-FU (fluorouracil, capecitabine)	118 (99.3)
	Oxaliplatin	111 (93.2)
	Irinotecan	87 (73.1)
	VEGF inhibitors (bevacizumab, aflibercept, ramucirumab)	68 (57.1)
	EGFR inhibitors (cetuximab, panitumumab)	35 (29.4)
	Regorafenib	11 (9.2)
	Trifluridine-tipiracil	2 (1.7)
	Other experimental drugs	3 (2.5)
	Other chemotherapy	8 (6.7)
	5FU-Oxa-Iri	82 (68.9)
Mutation status, n (%)	Both BRAF and KRAS wildtype	31 (26.1)
	BRAF mutation	30 (25.2)
	KRAS mutation	44 (37.0)
	Unknown	14 (11.8)
Tumour PD-L1 expression quantifiable at baseline, n (%)	≥1%	27 (26.5)
	<1%	75 (73.5)
	Unknown	17 (14.2)
Lynch syndrome****, n (%)	Yes	35 (29.4)
	No	35 (29.4)
	Unknown	49 (41.2)

*One patient had an ECOG performance status of 1 at randomisation that deteriorated to 3 by the time of treatment initiation.
**All patients (n=119) were disease stage IV at study entry
***One patient was allowed to enrol after refusing any cytotoxic chemotherapy.
****Lynch syndrome designation was based on the clinical records of the patients at sites in countries where this reporting was permitted (excluded Italy).

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B.2.6.1.2 Results

CheckMate 142 is currently ongoing. Initial results presented within this report are based on a database lock in February 2019, providing an overall minimum follow-up of ████████ ██████████████████████.[87] Efficacy endpoints related to tumour response were assessed by BICR and the investigator based on RECIST 1.1 criteria. Primary endpoint is ORR by investigator's assessment.

NIVO+IPI demonstrated clinically meaningful effect on efficacy endpoints including ORRs, DCR, DOR, PFS per investigator and per BICR and OS in patients with dMMR or MSI-H mCRC who had progression during or after, or have been intolerant to ≥1 prior anti-cancer treatment(s) for their metastatic disease. An ORR of ████████████████ per investigator assessment and ████████████████ per BICR was observed. DCR was ████ per investigator and ████ per BICR. Median PFS was ████ months per investigator and ████████ per BICR (Figure 6 and Figure 7, respectively) and median OS (Figure 8) and median DOR at the February 2019 DBL ██ The investigator assessed results are generally consistent with the BICR assessed results (Table 10). Percentage of patients achieving CR was ██. The 12-, and 24-month OS rates were 84.9% and ████, respectively.[82, 87]

Survival data presented here demonstrates meaningful OS benefit in the majority of patients treated with NIVO+IPI, who have received at least one prior line of therapy.

Table 10. CheckMate 142 results (February 2019 DBL)[82, 87]

Endpoint	NIVO+IPI (n=119) BICR assessed	NIVO+IPI (n=119) Investigator assessed
ORR, n (%) [95% CI]	████████████	████████████
DCR, n (%) [95% CI]	████████████	████████████
Best Overall Response		
Complete response, n (%) [95% CI]	████████████	████████████
Partial response, n (%) [95% CI]	████████████	████████████
Stable disease, n (%)	██████	██████
Progressive disease, n (%)	██████	██████
Unable to determine, n (%)	████	████
Duration of response (DOR)		

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Median (95% CI)	▮▮▮	▮▮▮
Patients with ongoing response, n (%)	▮▮	▮▮
Progression-free survival (PFS)		
Median, months (95% CI)	▮▮▮	▮▮▮
3 months, % (95% CI)	▮▮▮	NA
6 months, % (95% CI)	▮▮▮	▮▮▮
9 months, % (95% CI)	▮▮▮	NA
12 months, % (95% CI)	▮▮▮	71.6 (62.5, 78.9)
24 months, % (95% CI)	▮▮▮	▮▮▮
30 months, % (95% CI)	▮▮▮	NA
Overall survival (OS)		
Median, months (95% CI)	-	▮▮▮
3 months, % (95% CI)	-	▮▮▮
6 months, % (95% CI)	-	▮▮▮
9 months, % (95% CI)	-	87.4 (80.0, 92.2)
12 months, % (95% CI)	-	84.9 (77.1, 90.2)-
24 months, % (95% CI)	-	▮▮▮-
30 months, % (95% CI)	-	▮▮▮
BICR: blinded independent central review; CI: confidence interval; DBL: database lock; DCR: disease control rate; IPI: ipilimumab; NA: not available; NIVO: nivolumab; NR: not reached; ORR: objective response rate.		

As of the February 2019 database lock, ▮▮▮ of the 119 patients enrolled in the cohort of interest were continuing to receive treatment; the most common reason for discontinuing therapy was disease progression ▮▮▮. Patient disposition at the end of the treatment period is shown in Table 11.

Table 11. CheckMate 142: Patient disposition at the end of the treatment period[87]

	NIVO+IPI
	n (%)
Patients enrolled	▮
Patients continuing in the treatment period	▮▮
Patients not continuing in the treatment period	▮▮
Patients continuing in the study	▮▮
Patient no continuing in the study	▮▮

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Reason for not continuing in the treatment period (discontinuing treatment)		
Disease progression		██████
Study drug toxicity		██████
Death		████
Adverse event unrelated to study drug		████
Patient request to discontinue study treatment		████
Maximum clinical benefit		████
Other		████

Figure 6. Investigator-assessed progression-free survival: February 2019 database lock[82]

██

Figure 7. BICR-assessed progression-free survival: February 2019 database lock[82]

██

BICR: blinded independent central review; NA: not available.

Figure 8. Overall survival from CheckMate 142: February 2019 database lock

██

B.2.6.1.3 Health-related quality of life (HRQoL)

Of the 119 patients treated with NIVO+IPI in CheckMate 142, 107 patients were included in the patient reported outcomes (PRO) analysis. Two patients were excluded due to no PRO data available, 2 were excluded due to missing baseline assessment, and 8 were excluded due to missing post-baseline assessments.

B.2.6.1.3.1. EORTC QLQ-C30

The EORTC QLQ-C30 instrument was used in CheckMate 142 to assess HRQoL. The EORTC QLQ-C30 is a commonly used QoL instrument in oncology trials, with 30 items divided among 5 functional scales (physical, role, cognitive, emotional, and social), 9 scales measuring symptoms or concerns common to cancer patients (fatigue, pain, nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), and a global health/quality-of-life scale. Raw scores for the EORTC QLQ-C30 are transformed to a 0–100 metric such that higher values indicate better functioning or quality of life or a higher level of symptoms. Changes from baseline of at least 10 points for EORTC QLQ-C30 were considered clinically meaningful. [78]

EORTC QLQ-C30 was assessed prior to first dose on day 1 and every 6 weeks thereafter, with additional follow-up at follow-up visit 1 and 2.

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██ were reported in global quality of life, which were ██ in global quality of life were further recorded at ████████████████████. Figure 9 depicts the mean change from baseline global health status, showing a ██ results were observed for ██ ████ with clinically meaningful improvements from ████████████ with some outcomes being maintained ██████████████████████ Meaningful improvements for ██ were observed at ████████████████████████████ respectively, but were ██████████ across the assessment period. █meaningful improvements in ██████████████████████████████████████ were observed.[88]

Figure 9. EORTC QLQ-C30: Mean change from baseline in global health status[88]

█

B.2.6.1.3.2. EQ-5D-3L

The EQ-5D-3L instrument was used in CheckMate 142 to assess HRQoL. The EQ-5D-3L is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems. Using country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his/her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0–100 with 0 being the worst health state imaginable and 100 being the best health state imaginable.[78]

EQ-5D-3L was assessed ████████████████████████████ hereafter.[88] These results indicate that patients undergoing treatment with NIVO+IPI demonstrate ███████ in EQ-5D index scores and EQ-5D VAS compared with pre-treatment measurements at baseline. These ████████████████████████████ Figure 10 and Figure 11 depict the mean change from baseline for index scores and VAS, respectively, ████████████████████████████.[88]

Figure 10. EQ-5D-3L: Index score mean change from baseline[88]

Figure 11. EQ-5D-3L: VAS mean change from baseline[88]

B.2.7. Subgroup analysis

The investigator-assessed and BICR-assessed ORR using RECIST 1.1 were compared across baseline subgroups, including age, region, gender, race, KRAS/BRAF mutation status, baseline ECOG PS, time from initial diagnosis to first dose, primary tumour location, number of prior systemic regimens received, and time from completion of most recent prior therapy regimen to treatment. Results of these subgroup analyses are provided in Table 12. Based on BICR-assessed results, ████████████████ was noted in the response rate between the subgroups concerning age, time from initial diagnosis, primary tumour location, number of prior systemic regimen received, time from progression of most recent prior therapy to treatment and time from completion of most recent prior therapy regimen to treatment. For the remaining subgroups, ████████████████████████ Investigator-assessed results show ████████████████ in the response rate in subgroups concerning age, country, lynch syndrome, KRAS/BRAF mutation status, time from initial diagnosis, number of prior systemic regimen received, time from progression of most recent prior therapy to treatment and time from completion of most recent prior therapy regimen to treatment. For the remaining subgroups, ████████████████████[87, 89]

Furthermore, PFS and OS were assessed by KRAS/BRAF mutation status. For patients with KRAS mutation (███), median PFS was ████████████████████████ Median PFS ██████████ in any other KRAS/BRAF mutation subgroup (BRAF mutation, KRAS/BRAF

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Wild-type, Status Unknown). As of the February 2019 database lock, median OS was ▮▮▮▮▮▮▮ in any of the KRAS/BRAF mutation subgroups.[82, 87]

Table 12. CheckMate 142: Subgroup analysis of ORR by baseline characteristics[82, 87 57]

Stratification factor	ORR			
	BICR assessment		Investigator-assessed	
	n/N (%)	95% confidence interval[a]	n/N (%)	95% confidence interval[a]
Age				
<65 years	▮	▮	▮	▮
≥65 years	▮	▮	▮	▮
≥65 and <75 years	▮	▮	▮	▮
≥75 years	▮	▮	▮	▮
Gender				
Male	▮	▮	▮	▮
Female	▮	▮	▮	▮
Region				
US/Canada	▮	▮	▮	▮
Europe	▮	▮	▮	▮
Rest of world	▮	▮	▮	▮
Race				
White	▮	▮	▮	▮
Lynch syndrome				
Yes	▮	▮	▮	▮
No	▮	▮	▮	▮
Unknown	▮	▮	▮	▮
KRAS/BRAF mutation status				
KRAS/BRAF wild type	▮	▮	▮	▮
BRAF mutation	▮	▮	▮	▮
KRAS mutation	▮	▮	▮	▮
Unknown	▮	▮	▮	▮
Baseline ECOG performance status				
0	▮	▮	▮	▮
≥1	▮	▮	▮	▮
Time from initial diagnosis				
<1 year	▮	▮	▮	▮
1≤2 years	▮	▮	▮	▮
2<3 years	▮	▮	▮	▮
≥3 years	▮	▮	▮	▮
Primary tumour location				
Rectum	▮	▮	▮	▮
Left and sigmoid colon	▮	▮	▮	▮
Right colon	▮	▮	▮	▮
Transverse colon	▮	▮	▮	▮
Number of prior systemic regimen received				
1	▮	▮	▮	▮

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| Stratification factor | ORR | | | |
| | BICR assessment | | Investigator-assessed | |
	n/N (%)	95% confidence interval[a]	n/N (%)	95% confidence interval[a]
2	■	■	■	■
3	■	■	■	■
>=4	■	■	■	■
Time from completion of most recent prior therapy regimen to treatment				
< 3 months	■	■	■	■
3-6 months	■	■	■	■
>6 months	■	■	■	■
Time from progression of most recent prior therapy to treatment				
< 3 months	■	■	■	■
3-6 months	■	■	■	■
>6 months	■	■	■	■
[a]Confidence interval based on the Clopper and Pearson method.				
BICR: blinded independent central review; NA: not available; ORR: objective response rate.				

B.2.7.1. Baseline PD-L1 expression and efficacy

Patients were enrolled regardless of PD-L1 expression status; however, pre-study (baseline) tumour tissue specimens were systematically collected in order to conduct pre-planned analyses of efficacy according to PD-L1 expression status.

The ■ of patients had PD-L1 tested at baseline and of these, ■ had quantifiable PD-L1 expression at baseline. ■ of patients did not have quantifiable PD-L1 expression at baseline (including patients without baseline tumour sample and PD-L1 not evaluable). ■ patients had indeterminate PD-L1 expression at baseline. A total of ■ had quantifiable PD-L1 result: ■ patients had baseline PD-L1 ≤1%, and ■ patients had PD-L1 <1%; ■ patients had PD-L1 ≥5%, and ■ patients had PD-L1 <5%.

PD-L1 was not used as stratification factor in CheckMate 142. Efficacy was observed regardless of tumour PD-L1 expression (Table 13).

Table 13. CheckMate 142: Response by PD-L1 expression group[82]

| | Response by PD-L1 expression group | | | |
| | BICR assessment | | Investigator-assessed | |
	≥1% (n=27)	<1% (n=75)	≥1% (n=27)	<1% (n=75)
ORR, % (95% CI)	■	■	■	■
CR, %	■	■	■	■
PR, %	■	■	■	■
PFS*, months (95% CI)	■	■	■	■
OS*, months (95% CI)	■	■	■	■
*Median PFS.				

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	Response by PD-L1 expression group			
	BICR assessment		Investigator-assessed	
	≥1% (n=27)	<1% (n=75)	≥1% (n=27)	<1% (n=75)
BICR: blinded independent central review; CR: complete response; NA: not available; ORR: objective response rate; PFS: progression-free survival; PR: partial response.				

B.2.8. Meta-analysis

Comparative clinical efficacy would ideally be drawn from randomised controlled trials with active comparators. Where these are not available, the standard approach would be to conduct a network meta-analysis. However, given the final evidence base (CheckMate142) doesn't provide a common comparator linking NIVO+IPI with comparators of interest, traditional ITC methods using anchored comparisons cannot be applied.

B.2.9. Indirect and mixed treatment comparisons

Key points

- In the absence of a control arm for CheckMate 142, indirect treatment comparison using standard methodologies (e.g. network meta-analysis) are not possible. For this reason, an unanchored matching-adjusted indirect comparison is required.

- Based on the SLR, weighted mean of reported values for comparator median OS was 9.48 months while median OS for NIVO+IPI was not reached despite ████████████████. Similarly, weighted mean of reported comparator values was 34.91% for OS at one year, compared with 85% for NIVO+IPI.

- In the unadjusted ITC, mean OS for NIVO+IPI was ███ months, compared with 7.22–17.32 months for comparators. Similarly, mean PFS was ███ months versus 1.83–6.79 months, respectively.

- Applying MAIC methodology, comparator mean OS ranged from 7.13 months to 17.06 months, while mean PFS ranged from 1.81 months to 6.92 months. By comparison, NIVO+IPI provided mean OS of ███ months and mean PFS of ███ months.

- The primary limitation of this analysis is the lack of evidence in the MSI-H/dMMR mCRC population. Although, this evidence was sought, it was not available to inform the MAIC. Clinical experts believe that the MSI-H/dMMR patients may have worse outcomes than the overall population, indicating that this analysis may be conservative.

Comparative clinical efficacy would ideally be drawn from randomised controlled trials (RCTs) for nivolumab plus ipilimumab versus all relevant comparators. However, when RCT evidence is not available, the standard approach would be to conduct an indirect comparison. Standard

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methods for indirect comparisons, for example, network meta-analysis (NMA), require indirect comparisons to be made via common comparator treatments (however, this was not possible). Hence, the available evidence base requires alternative methods of indirect comparison.

Matching adjusted indirect comparisons (MAIC) allow for adjustments in cross-study differences in baseline characteristics that may act as treatment effect modifiers, as well as to allow for comparisons in the situation whereby treatments of interest are not linked via common comparators. MAIC utilises patient-level data (PLD) in one study (index study) and aggregate summary data from another study (target study). Data in the index study is weighted to reflect that of the target study and patient-level outcomes based upon these weighted data are compared to the aggregate summaries for outcomes reported in the target study, to provide a measure of comparative effectiveness which has been adjusted for differences between the patient populations in the two studies.

As use of MAICs has increased over time, the NICE Decision Support Unit has published a technical support document that examines methods for population-adjusted indirect comparisons and makes recommendations on the use of these methods in submissions to NICE.[90] MAIC analyses undertaken as part of this study will be conducted in line with these guidelines on unanchored comparisons. Despite availability of this methods guide, limitations are still inherent in the MAIC methodology, and these are explored in Section B.2.9.2.4.

B.2.9.1. Systematic literature review

As outlined in Section B.2.1.1, an SLR was undertaken to identify published estimates of effectiveness for comparators of interest. A full description of methods used to conduct these SLRs is provided in Appendix D.

Outcomes for NIVO+IPI significantly exceed outcomes for all other comparators. The weighted mean of reported median OS value was 9.48 months for comparators overall (range: 6.05 months to 12.73 months), while median OS for NIVO+IPI was not reached despite ████████████████████████. Similarly, weighted mean of reported values was 36.33% for OS at one year, compared with 85% for NIVO+IPI. Furthermore, PFS outcomes tended to be higher for NIVO+IPI compared with comparator therapies (Table 14). Outcomes are also depicted in Figure 12, Figure 13 and Figure 14.

As can be seen, FOLFIRI and FOLFOX appear to be most efficacious, with BSC, raltitrexed and trifluridine-tipiracil associated with worst outcomes. Most studies reported median OS around 12 months, and almost all studies reported median OS below 24 months. One outlier study was identified, providing median OS over 24 months: one phase 2 trial assessing two FOLFIRI dosing schemes (n=68) identified median OS of 28 months in one arm and median OS of 18 months in the other.[91]

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Figure 12. Median overall survival for relevant comparators as identified by the systematic literature review
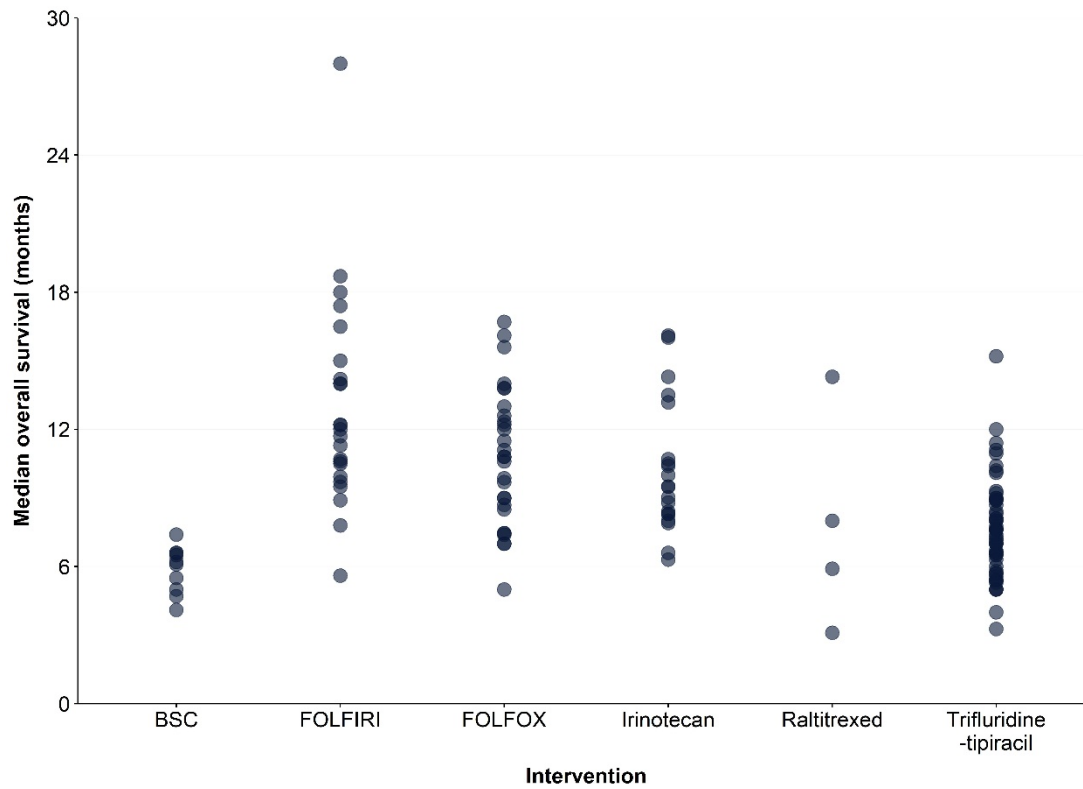
Figure 13. Overall survival at one year for relevant comparators as identified by the systematic literature review

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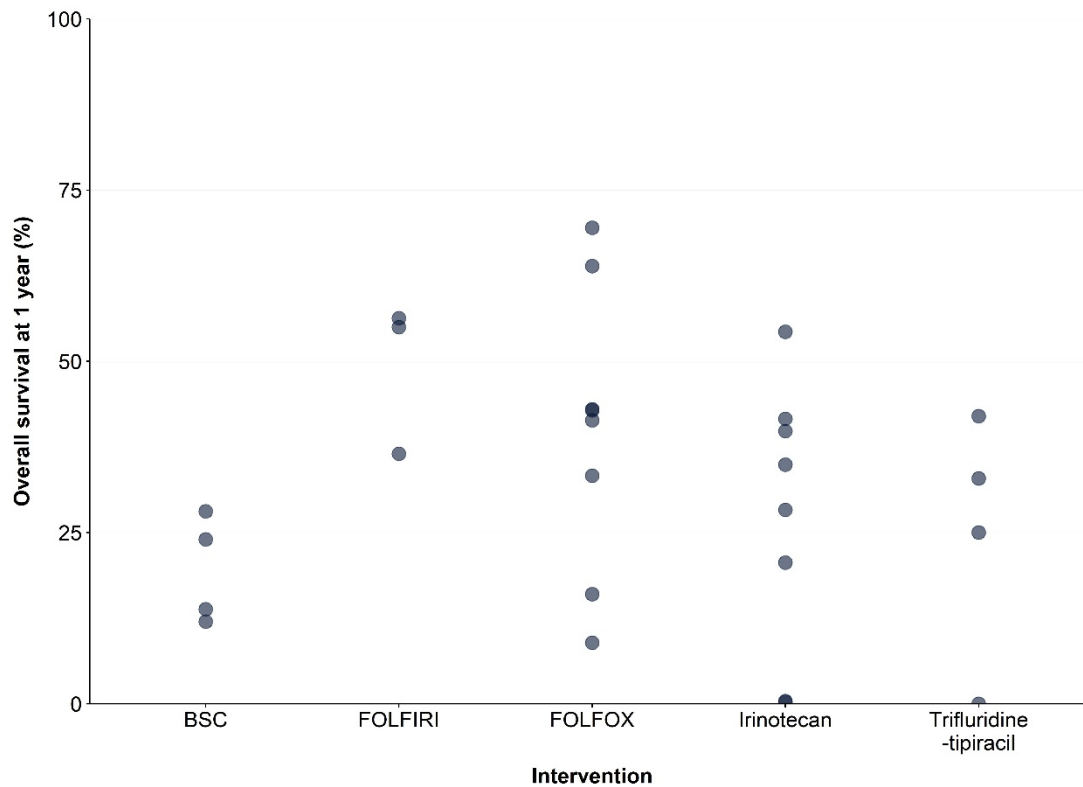
Figure 14. Median progression-free survival for relevant comparators as identified by the systematic literature review

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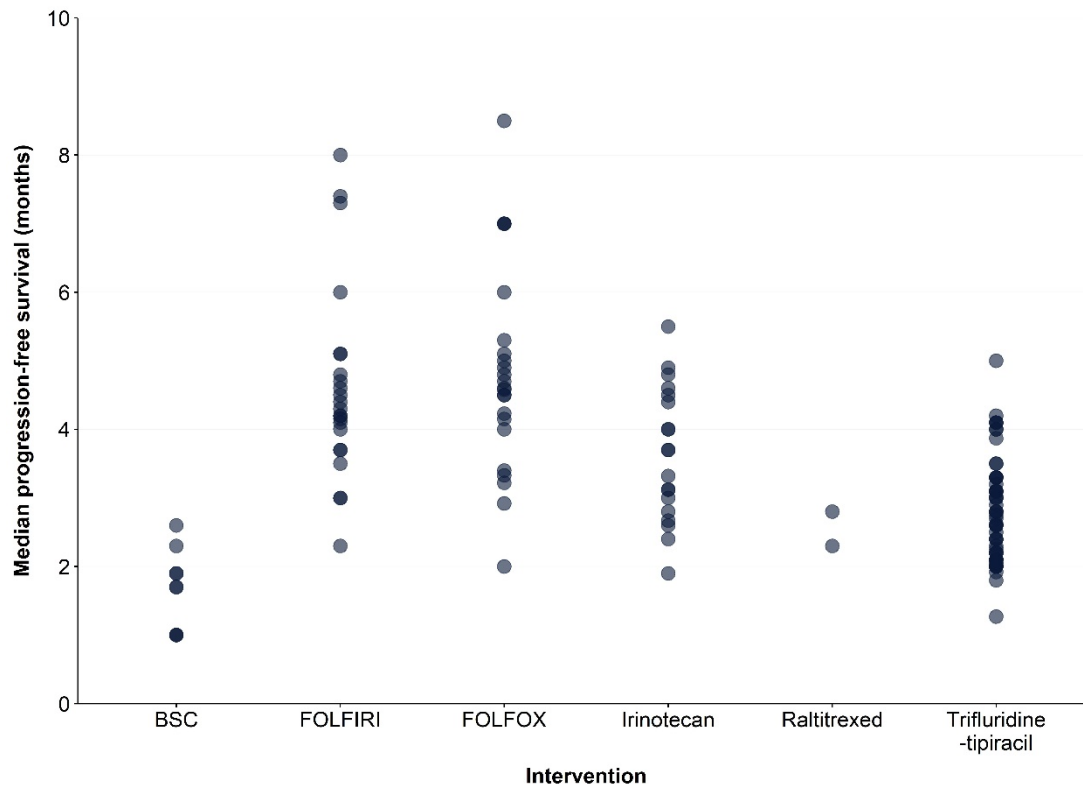
Table 14. Comparison of SLR outcomes with NIVO+IPI outcomes

		Overall survival			Progression-free survival		
		Median (months)	**One year (%)**	**Two years (%)**	**Median (months)**	**One year (%)**	**Two years (%)**
Nivolumab plus ipilimumab*	Weighted mean	Not reached	85	77.17	Not reached	71.1	60
	Minimum	Not reached	85	74	Not reached	71	60
	Maximum	Not reached	85	83.8	Not reached	71.3	60
Comparators overall	Weighted mean	9.48	34.91	NR	3.27	6.52	NR
	Minimum	3.1	0	NR	0.99	6.52	NR
	Maximum	28	69.5	NR	8.5	6.52	NR
FOLFIRI	Weighted mean	12.73	50.05	NR	4.52	6.52	NR
	Minimum	5.6	36.5	NR	2.3	6.52	NR
	Maximum	28	56.31	NR	7.4	6.52	NR
FOLFOX	Weighted mean	11.92	43.4	NR	4.87	NR	NR
	Minimum	5	8.9	NR	2	NR	NR
	Maximum	19.3	69.5	NR	8.5	NR	NR
Irinotecan monotherapy	Weighted mean	10.44	35.12	NR	3.46	NR	NR
	Minimum	6.3	0.25	NR	1.9	NR	NR
	Maximum	16.1	54.3	NR	8	NR	NR
Raltitrexed	Weighted mean	6.32	NR	NR	2.39	NR	NR
	Minimum	3.1	NR	NR	2.3	NR	NR
	Maximum	14.3	NR	NR	2.8	NR	NR
Trifluridine-tipiracil	Weighted mean	7.89	34.98	NR	2.61	NR	NR
	Minimum	3.27	0	NR	1.27	NR	NR
	Maximum	15.2	42	NR	5	NR	NR
BSC/placebo	Weighted mean	6.05	22.66	NR	1.71	NR	NR
	Minimum	4.1	12	NR	0.99	NR	NR
	Maximum	7.4	28.1	NR	2.6	NR	NR
*This table presents SLR results only. Therefore, the most recent data cut of CheckMate142 is not included here.							

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B.2.9.2. Indirect treatment comparison

Clinical outcomes from the SLR provide an indication of the potential efficacy range associated with comparators of interest. However, as there are currently no data providing direct comparative evidence for NIVO+IPI in CheckMate 142 versus treatments of interest, indirect comparisons were required to inform the comparative effectiveness.

Full indirect treatment comparison methods and results are provided in Appendix L. A summary of the methods is provided below.

- **Comparators of interest**: In line with the NICE final scope, the following comparators were considered:

    o BSC

    o FOLFIRI

    o FOLFOX

    o Irinotecan monotherapy

    o Raltitrexed

    o Trifluridine-tipiracil

- **Outcomes of interest**: The following outcomes of interest were considered relevant to consideration of effectiveness:

    o OS – the time from randomisation or first exposure to study drug until death by any cause. If death is unobserved, patients are censored at most recent survival follow-up.

    o PFS – the time from randomisation or first exposure to study drug until the earlier of clinical progression or death. Patients receiving subsequent therapy are censored when commencing subsequent therapy. Patients not observed to die, progress or commence subsequent therapy are censored at most recent assessment time.

- Study selection: Studies identified from the SLR were assessed to identify robust and relevant sources of evidence for each comparator. Robustness and relevance of the evidence was judged on the following criteria:

    o Study design, where preference was given to:

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- Clinical trial evidence (i.e. not observational studies), preferably randomised controlled trials

- Studies pivotal to marketing authorisation

- Previous submission to NICE

  - Study size, with preference given to larger patient populations

  - Patient populations similar to the CheckMate 142 NIVO+IPI population

  - Availability of survival outcomes data

- Unadjusted comparison: Following selection of relevant evidence for each comparator, Kaplan-Meier data for OS and PFS were digitised and parametric extrapolations were derived to provide estimates of mean survival.

- Matching-adjusted indirect comparisons: individual patient data from CheckMate 142 was reweighted to match the baseline characteristic summary statistics from the comparator cohort. Patient-level outcomes were similarly weighted by these values to provide an estimate of the outcomes that would have been observed should patients, equivalent to those in the comparator trial, have been randomised to the arms of the index trial.

B.2.9.2.1 *Unadjusted indirect treatment comparison*

Full description of methods and results for the unadjusted indirect comparison are provided in Appendix L. As outlined above, following selection of relevant evidence for each comparator, OS and PFS Kaplan-Meier data were digitised and parametric extrapolations were derived to provide estimates of mean survival. For FOLFIRI and irinotecan, two studies were assessed, due to equivalent relevance. Additionally, the RECOURSE study included a prespecified regional subgroup analysis, which revealed better outcomes for PFS and OS for both the BSC plus placebo and trifluridine-tipiracil plus BSC arms in Japan compared with European and US patients; as a result of this, and as CheckMate 142 did not recruit patients from Japan, comparisons were undertaken to the European and US subgroups only.

A summary of mean survival outcomes is provided in Table 15. As can be seen, these are aligned with outcomes from Table 14.

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Table 15. Unadjusted indirect treatment comparison outcomes - NIVO+IPI versus comparator interventions of interest

Intervention	N	Overall Survival (months)	Progression-free survival (months)
		Mean	Mean
NIVO+IPI	119	███	██
FOLFIRI[92, 93]	536	16.23	6.62
	614	15.70	6.79
FOLFOX[94]	429	17.32	5.47
Irinotecan monotherapy[95, 96]	650	13.27	3.57
	335	14.57	5.57
Raltitrexed[97]	18	8.51	4.04
Trifluridine-tipiracil[61]	271	10.39	3.68
	64	11.71	3.63
BSC[61]	132	7.22	1.83
	35	8.07	1.87

B.2.9.2.2 Matching-adjusted indirect comparison

B.2.9.2.2.1. Comparison of unanchored comparison methodologies

Whilst both MAIC and simulated treatment cohort (STC) may be applicable in this scenario, the advantages of MAIC were chosen over STC. STC has the benefit of being rapidly applicable to a large number of comparators, once suitable outcome equations have been generated. Developing each of these equations is a drawback if one has a large number of outcomes to compare across. This is particularly pertinent for time-to-event data, where the applicability of a proportional hazards or accelerated failure time model on each covariate must be assessed; interactions between covariates or time-dependency of cofactors must be considered; and the general consideration that if a population is made up of several distinct sub-populations with differing hazard profiles, an estimation in the mean is not likely to capture the outcome well. By contrast, MAIC brings the benefit of not imposing a fixed distribution on the resulting outcome, allowing non-parametric models to still be applied, or, where parametric modelling is required, the variation of as many parameters as necessary to capture the characteristics of the effective sub-population you are modelling. This is pointed out in Ishack (2015)[98]:

> *"MAIC also offers flexibility for the analyses of time-to-event outcomes and those requiring non-linear models (such as logistic or time to event), or in situations where the predictive equations derived for STC offer poor fit"*

B.2.1.1.1.1. MAIC methodology

Full methodology is provided in Appendix L; in brief, this method, as described by Signorovitch (2010)[99], reweights individual patient data in the intervention trial (CheckMate 142) such that

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the weighted baseline characteristic summary statistics experienced by MSI-H patients receiving NIVO+IPI match the summary statistics reported for patients receiving comparator. The patient-level outcomes are then similarly weighted by these values and provide an estimate of the outcomes that would have been observed should patients, equivalent to those in the comparator trial, have been randomised to the arms of the index trial.

The stages of MAIC applied for the present analysis are outlined in Figure 15. In brief, they are as follows:

- Exclude from the index study (CheckMate 142) any patients who could not be present in the comparator study due to design (form overlap).

- Form a series of weights using the method of moments such that each of the matched aggregate measures of prognostic variables in the comparator trial is equalled by the weighted aggregate measure in the index study.

- Apply these weights to the outcomes in the index study.

- Compare the weighted outcomes of the index study to those reported in the comparator study.

- Transport the relative treatment effect onto the population of interest, represented by CheckMate 142.

Potential matching variables were determined by consultation with clinical experts and with reference to the availability of aggregate data from comparator studies. Three adjustment sets were ultimately determined:

- **Primary: Predictive + demographic** – A subset of available variables identified through a process of forward stepwise selection of predictive variables within a Cox proportional hazards model, maximising partial likelihood in 10-fold cross validation, plus age and sex, deemed necessary for inclusion in extrapolation given the lifetable component of the survival models of NIVO+IPI, irrespective of their prognostic relevance in the within-trial period to which the Cox models were fitted.
- **Fallback: Demographic** – Age and sex alone, providing a fallback model in case of overly-concentrated patient weights.
- **All** – All available prognostic factors of the above defined list. Full matching was not expected to be possible for all studies upon all factors given the limited study size of CheckMate 142, and so this was expected to be a scenario analysis for a limited set of comparisons only.

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Figure 15. The MAIC process (after Atkins et al. Immunotherapy, volume 11, 2017.)[100]
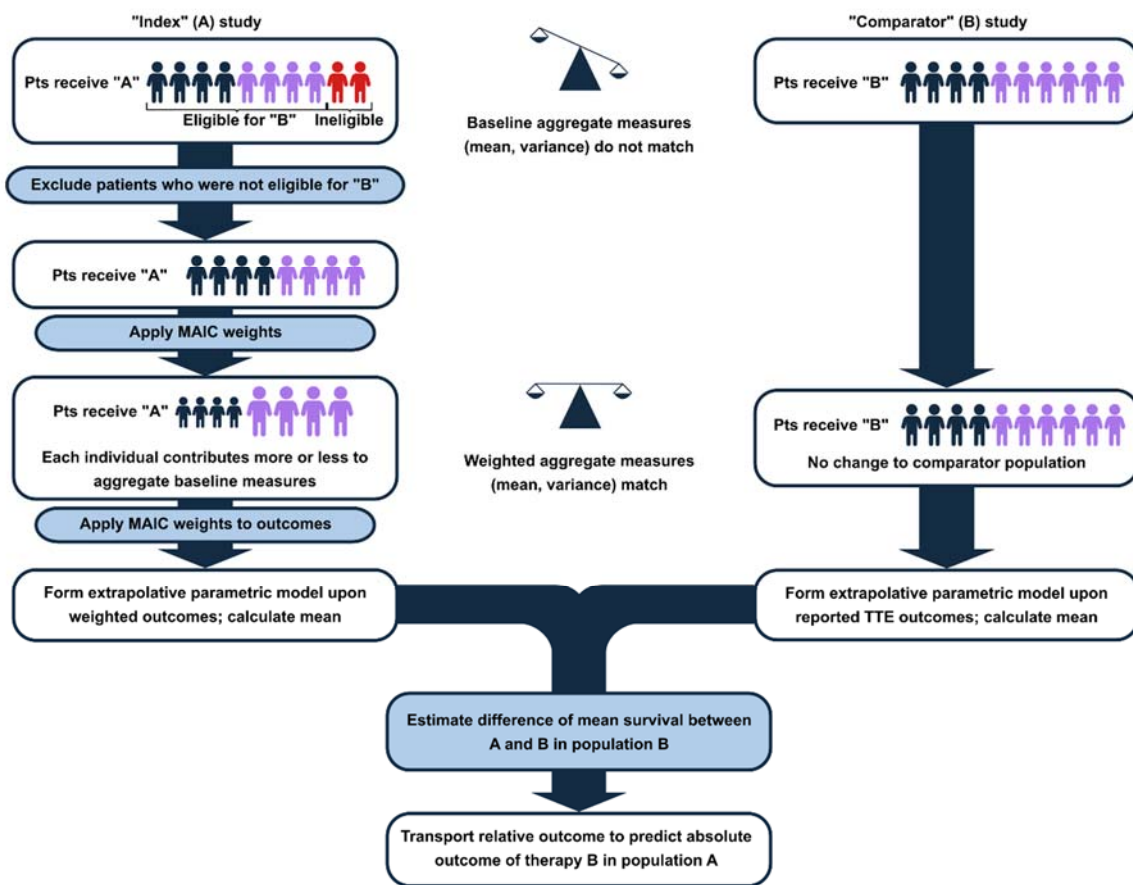
MAIC can serve to reduce the bias inherent in unanchored comparisons, particularly in naïve indirect comparisons; however, it cannot remove all bias in the presence of unreported or otherwise unknown confounding variables. In this analysis, the magnitude of expected bias reduction in the outcome estimation was demonstrated by multiplying the cox linear coefficients by the difference in mean covariates between the studies.

B.2.1.1.1.2.   MAIC results

The adjustment of NIVO+IPI data is depicted in Figure 16 to Figure 21. It should be noted that the impact of this adjustment is used to calculate treatment effect and is transported to the CheckMate 142 NIVO+IPI population (i.e. effect of comparator on CheckMate 142 patients is calculated so comparator survival varies while NIVO+IPI survival remains static). Outcomes after transportation of the treatment effect are summarised in Table 16. The small sample size of the relevant population in CheckMate 142 prevented adjustment by a large number of prognostic variables, and in many cases a minimal matching set of age and sex was used.

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Adjustment of the CheckMate 142 data did not result in drastically different outcomes for any matching set, unless weights were concentrated in a very small number of individuals. The uncertainty in the comparisons was overwhelmingly due to the absolute uncertainty over the CheckMate 142 mean survival, with little increase in variance for the chosen matching set. The comparator data was in general mature and the mean survival was subject to a low standard error.

Both OS and PFS were considerably improved with NIVO+IPI relative to all comparators of interest.

Patients on comparator studies tended to be older, but there were few other generalisations that could be made to the populations. There were a number of studies specific to second line; in comparison to these studies, residual bias was expected to favour the comparator. Among the comparators, there was no bias towards outcomes improving or worsening for the adjusted NIVO+IPI patients.

Of particular note, evidence for raltitrexed was extremely sparse. Only, one relevant study describing raltitrexed monotherapy evidence was identified. This study was a retrospective review of eighteen mCRC patients aged 70 years and over, available as an abstract only. In this case, enough data in the CheckMate 142 elderly subgroup were not available, and the effective study size was substantially reduced. Due to this low study size and the limited age range of the analysis, the treatment effect thus calculated was not suitable for calibration to the CheckMate 142 population. Therefore, an unadjusted comparison was used in the base case.

Despite this, outcomes for other therapies were comparable to unadjusted outcomes from the SLR. FOLFIRI provided mean OS of 15.3-17.2 months, compared with weighted mean of median OS values of 12.4 months from the SLR. Similarly, FOLFOX provided mean OS of 15.7 months compared with median OS of 11.9 months, BSC provided mean OS of 7.2-8.1 months compared with median OS of 6.1 months, irinotecan provided mean OS of 13.3-15.4 compared with median OS of 10.8 months and trifluridine-tipiracil provided mean OS of 10.7-11.7 months compared with median OS of 8.0 months. Hence, these values can be considered plausible.

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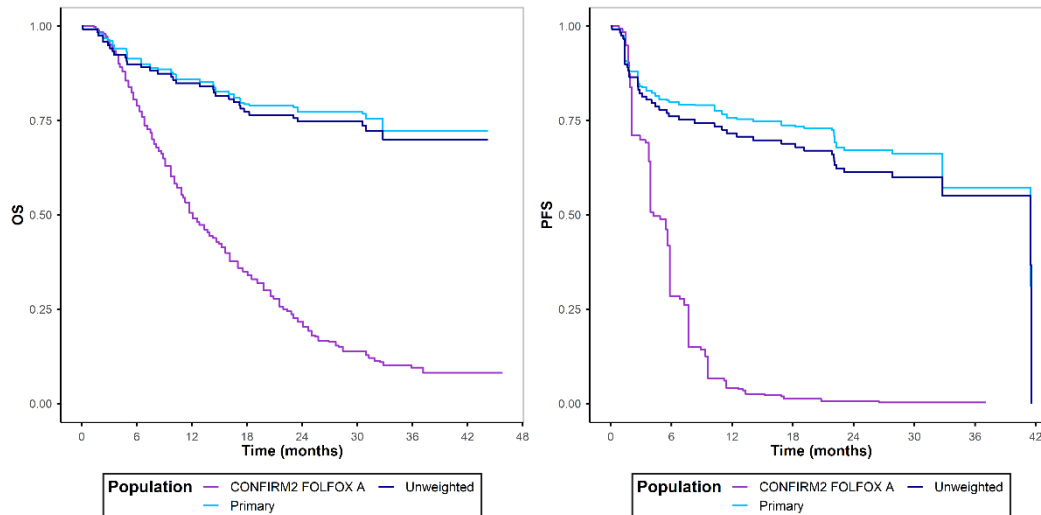
Figure 16. NIVO+IPI versus FOLFOX: OS (left) and PFS (right) estimated through the MAIC between CheckMate 142 and CONFIRM 2
Purple depicts FOLFOX; all other colours depict NIVO+IPI KM, unweighted or weighted
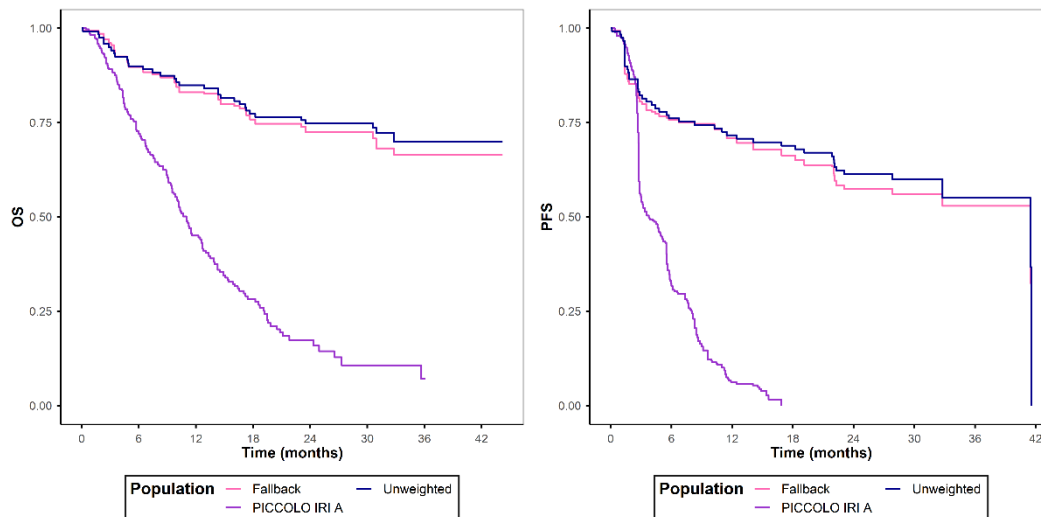
Figure 17. NIVO+IPI versus irinotecan monotherapy: OS (left) and PFS (right) estimated through the MAIC between CheckMate 142 and PICCOLO
Purple depicts irinotecan KM; all other colours depict NIVO+IPI KM, unweighted or weighted. "Primary" and "All" matching sets are coincident

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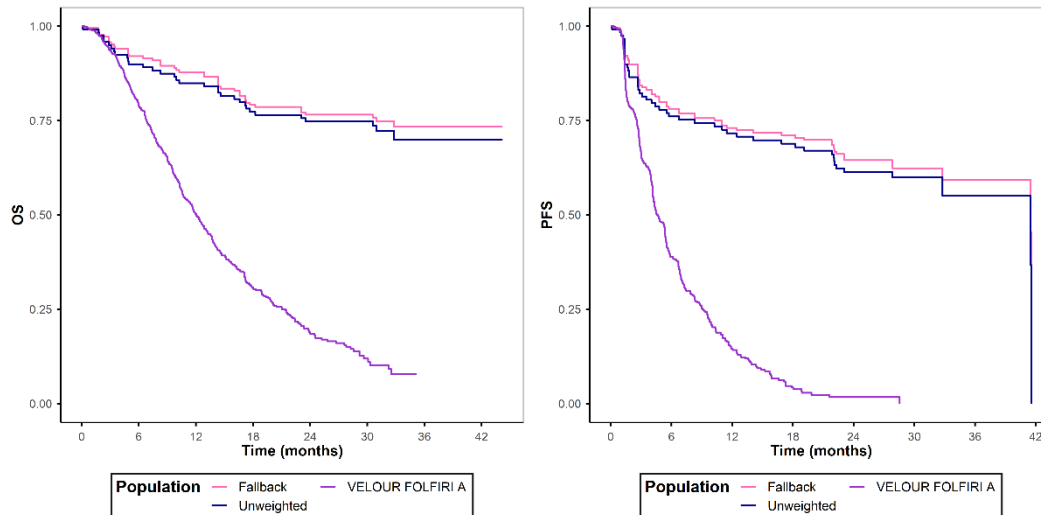
Figure 18. NIVO+IPI versus FOLFIRI: OS (left) and PFS (right) estimated through the MAIC between CheckMate 142 and VELOUR
Purple depicts FOLFIRI KM; all other colours depict NIVO+IPI KM, unweighted or weighted
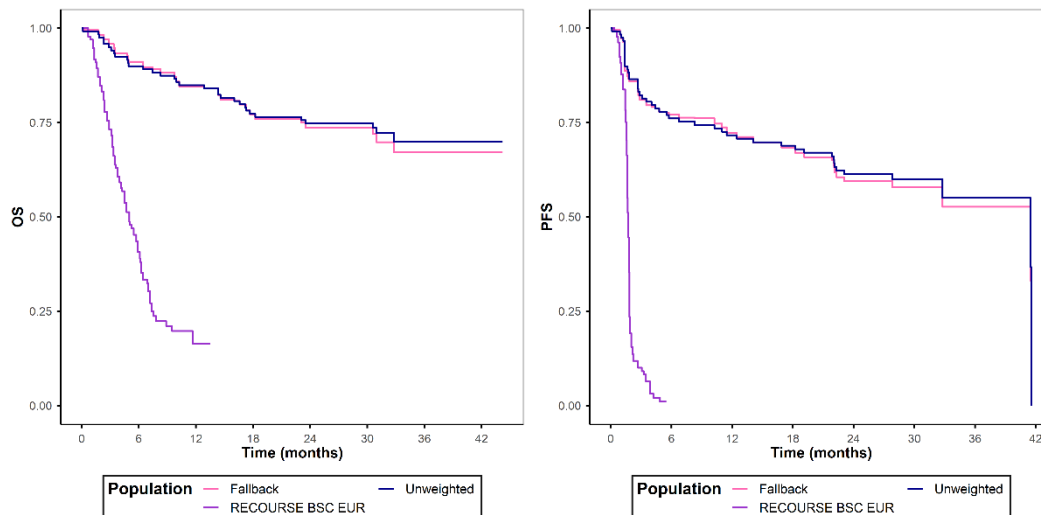
Figure 19. NIVO+IPI versus BSC: OS (left) and PFS (right) estimated through the MAIC between CheckMate 142 and European subgroup from the RECOURSE BSC arm
Purple depicts BSC KM; all other colours depict NIVO+IPI KM, unweighted or weighted

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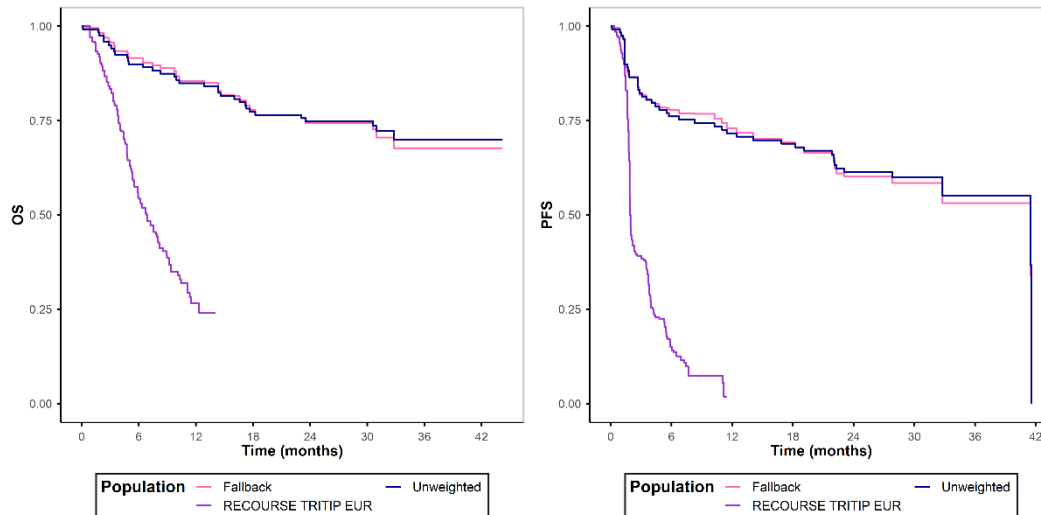
Figure 20. NIVO+IPI versus Trifluridine-tipiracil: OS (left) and PFS (right) estimated through the MAIC between CheckMate 142 and European subgroup from the trifluridine-tipiracil arm of RECOURSE

Purple depicts trifluridine-tipiracil KM; all other colours depict NIVO+IPI KM, unweighted or weighted
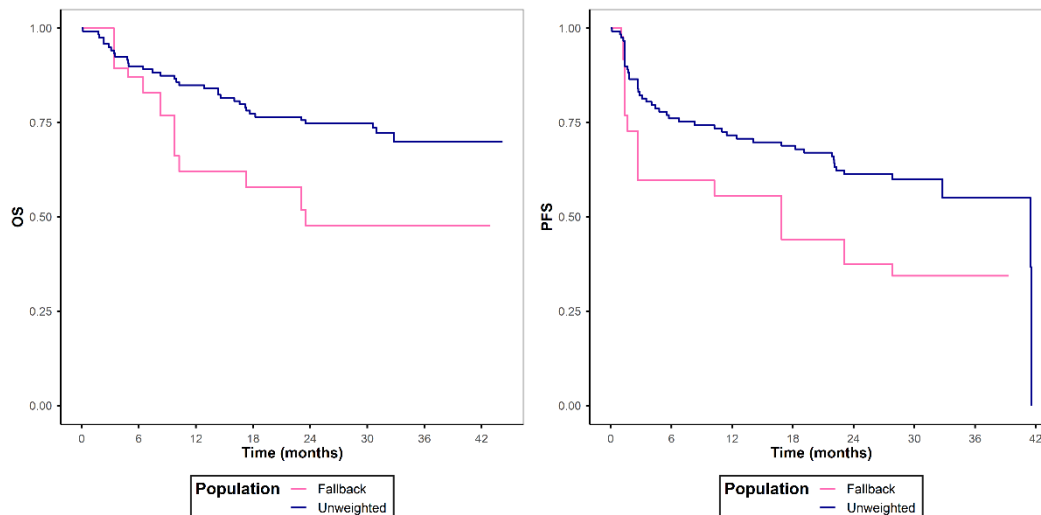
Figure 21. NIVO+IPI versus raltitrexed: OS (left) and PFS (right) estimated through the MAIC between CheckMate 142 and Ugidos et al.

No KM is available for raltitrexed; mean OS values for this study are based on median OS data. Unweighted KM was used for base-case given spurious results following matching

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Table 16. Summary of outcomes informing the base case comparison: unadjusted and adjusted indirect treatment comparison

Intervention	Study	N	OS (months)				PFS (months)			
			Unadjusted mean	Covariate set	Effective sample size	Adjusted mean	Unadjusted mean	Covariate set	Effective sample size	Adjusted mean
NIVO+IPI	CheckMate 142 *	119	███				███			
FOLFIRI	RAISE[92]	536	16.23	Fallback	98.4	17.19	6.62	Fallback	98.4	7.54
	VELOUR[93] *	614	15.70	Fallback	96.8	15.30	6.79	Fallback	96.8	6.33
FOLFOX	CONFIRM2[94] *	429	17.32	Primary	75.9	15.65	5.47	Primary	75.9	4.49
Irinotecan monotherapy	EPIC[95]	650	13.27	Primary	110.9	13.31	3.57	Primary	110.9	3.80
	PICCOLO[96] *	335	14.57	Fallback	98.8	15.42	5.57	Fallback	98.8	6.69
Raltitrexed	Ugidos et al[97] *	18	8.51	Fallback	16.2	20.41	4.04	Fallback	16.2	8.63
Trifluridine-tipiracil	RECOURSE/EUR[61] *	271	10.39	Fallback	96.5	10.86	3.68	Fallback	96.5	4.19
	RECOURSE/USA[61]	64	11.71	Fallback	106	11.70	3.63	Fallback	106	3.70
BSC	RECOURSE/EUR[61] *	132	7.22	Fallback	97.5	7.55	1.83	Fallback	97.5	2.10
	RECOURSE/USA[61]	35	8.07	Fallback	106.4	8.13	1.87	Fallback	106.4	1.90

*Applied in the base case

Note: The most comparable data sources from the SLR were sought to inform the comparators for each comparator therapy. The RECOURSE study included a prespecified regional subgroup analysis, which revealed better outcomes for PFS and OS for both the BSC plus placebo and trifluridine-tipiracil plus BSC arms in Japan compared with European and US patients; as a result of this, and as CheckMate 142 did not recruit patients from Japan, comparisons were undertaken to the European and US subgroups only, with the European subgroup forming the base case. Only one source of survival data was available for Raltitrexed, which was undertaken in an elderly population and the resulting effective sample size of the matched population was severely compromised. The adjusted results were not used in the base case.

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B.2.9.2.3 Conclusion from available clinical evidence

A summary of clinical evidence for NIVO+IPI (CheckMate 142) and relevant comparators for metastatic MSI-H CRC following prior therapy is shown in Table 14 and an overview of the benefit associated with NIVO+IPI in terms of predicted mean OS and PFS is shown in Table 16.

The evidence comparing CheckMate 142 and relevant comparators show significant clinical benefit for NIVO+IPI-treated patients over FOLFIRI, FOLFOX, irinotecan, raltitrexed, trifluridine-tipiracil, and BSC for the treatment of patients with metastatic MSI-H CRC following prior therapy.

B.2.9.2.4 Uncertainties in the indirect and mixed treatment comparisons

Comparative clinical efficacy would ideally be drawn from randomised controlled trials with active comparators, and where these are not available, the standard approach would be to conduct a network meta-analysis. However, a common anchor arm is absent because of the non-comparative design of CheckMate 142, precluding traditional indirect comparison methodology. Thus, in order to inform comparative efficacy, it is necessary to use alternative techniques, such as those applied within this study. In order to aid robustness and transparency, the NICE DSU has provided guidelines detailing best practice for adjusted indirect comparisons, such as MAIC.[101] This analysis was conducted and validated using these guidelines.

There are several limitations of these analysis that should be noted in order to provide appropriate context for these results. The primary limitation is that none of the SLR-identified studies enrolled entirely MSI-H CRC patients, or reported outcomes in this patient population, with the exception of studies assessing nivolumab. By contrast, CheckMate 142 required MSI-H status for enrolment into the NIVO+IPI arm. As such, this baseline characteristic cannot be fully adjusted for when undertaking a MAIC. A comparison of CheckMate 142 with outcomes from the overall mCRC population may be considered conservative, as outcomes may be poorer in mCRC patients with MSI-H/dMMR status; a full description of the available evidence is provided in Section B.1.3.2. In support of this, clinicians agree that patients with MSI-H mCRC likely have worse outcomes than the overall population of mCRC patients.[1] Further, a retrospective real-world study in the UK demonstrated that ███ over the study period of ██████████████████████████.[55] However, it can be acknowledged that the lack of MSI-H mCRC evidence adds uncertainty to the evaluation.

The MAIC technique attempts to adjust for differences in baseline characteristics between studies to allow for comparison. This method is reliant on reporting of baseline characteristics;

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where substantial differences in baseline populations were apparent or where no covariates were available for adjustment, studies were excluded from the MAIC analysis. However, if one covariate from the set were reported, the study was included in this analysis, with adjustment undertaken on this covariate alone, resulting in limited adjustment of outcomes. Further, it is possible that studies were included within the comparison due to lack of reporting of covariates where there was significant difference between the reference study and the target study. This is in common with all studies where variables may be unobservable; removal of bias due to these factors is not possible within MAIC.

Of particular note, evidence for raltitrexed was extremely sparse. Only, one relevant study describing raltitrexed monotherapy evidence was identified. This study was a retrospective review of eighteen mCRC patients aged 70 years and over, available as an abstract only. In this case, sufficient data in the CheckMate 142 elderly subgroup were not available and the effective study size was substantially reduced. Due to this low study size and the limited age range of the analysis, the treatment effect thus calculated was not suitable for calibration to the CheckMate 142 population and an unadjusted comparison was used in the base case.

Despite this, outcomes for other therapies were comparable to unadjusted outcomes from the SLR. FOLFIRI provided mean OS of 15.3-17.2 months, compared with weighted mean of median OS values of 12.4 months from the SLR. Similarly, FOLFOX provided mean OS of 15.7 months compared with median OS of 11.9 months, respectively, BSC provided mean OS of 7.2-8.1 months compared with median OS of 6.1 months, irinotecan provided mean OS of 13.3-15.4 compared with median OS of 10.8 months and trifluridine-tipiracil provided mean OS of 10.7-11.7 months compared with median OS of 8.0 months. Hence, these values can be considered plausible.

MAIC can only serve to reduce the bias inherent in unanchored comparisons, but it cannot remove all bias in the presence of unreported or otherwise unknown confounding variables. The analysis undertaken here has been permissive, allowing data where covariates are unreported to be assumed distributed as in the index study, and all covariations are derived from the index study as these are poorly reported in summary outcomes. As such, the bias in both the adjusted and unadjusted indirect comparison, whilst minimised within the MAIC, cannot completely be eliminated.

Despite these limitations, this ITC has been undertaken in a robust and transparent manner, with all relevant methodology and results reported. NIVO+IPI is associated with survival benefit across analyses, including analyses where there is an implausibly large increase in comparator survival due to low effective study size (i.e. raltitrexed MAIC comparison). Further, this survival benefit is unrelated to extrapolation of survival data; when survival at time points was assessed based on clinical trial evidence, NIVO+IPI was associated with substantial OS and PFS benefit that was apparent by 12 months and maintained at 24 months.

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B.2.10. Adverse reactions

Key points

- Based on available evidence, the safety profile of nivolumab and ipilimumab can be considered manageable, and acceptable in the context of alternative therapies, such as standard chemotherapy regimens.

- No new safety concerns were identified for nivolumab and ipilimumab. Overall, adverse events were consistent with the established safety profile of nivolumab with ipilimumab in other tumour types.

B.2.10.1. CheckMate 142

Safety data from CheckMate 142 was taken from the February 2019 database lock.[82]

B.2.10.1.1 Extent of exposure

As of the Feb-2019 DBL, a total of ▮▮▮▮▮▮▮ of patients received 90% to <110% of the planned dose intensity of nivolumab and ipilimumab, respectively. The median number (min, max) of doses received was ▮▮▮▮▮ for nivolumab and ▮▮▮▮▮ for ipilimumab. Note: the number of ipilimumab doses administered in combination with nivolumab was 4 per protocol.[82] The median duration of therapy based on Kaplan-Meier analysis was ▮▮▮▮▮. As of the Feb-2019 DBL, the maximum duration of therapy was ▮▮▮▮▮▮▮▮▮▮ for nivolumab and ipilimumab, respectively.[82]

Table 17. CheckMate 142: extent of exposure to study drugs (February 2019 DBL)[82]

Variable	All patients N=119	
	Nivolumab	**Ipilimumab**
Number of doses received		
Mean (SD)	▮▮▮▮▮	▮▮▮▮
Median (Range)	▮▮▮▮	▮▮▮▮
Cumulative dose (mg/kg)		
Mean (SD)	▮▮▮▮▮	▮▮▮▮▮
Median (Range)	▮▮▮▮▮▮	▮▮▮▮▮▮
Relative dose intensity (n)		
≥110%, n (%)	▮	▮
90–110%, n (%)	▮▮▮▮	▮▮▮▮▮
70–90%, n (%)	▮▮▮▮	▮▮▮▮
50–70%, n (%)	▮▮▮	▮▮▮
<50%, n (%)	▮	▮

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B.2.10.1.2 Overall adverse events

Any-grade, all-causality adverse events (AEs) occurred in ███ of patients. The most common AEs were ███ All causality Grade 3-4 AEs occurred in ███ of patients. The most common Grade 3-4 AEs were ██

███████[82]

██

███████████████████████████████.[82]

B.2.10.1.3 Serious adverse events

All-causality serious adverse events (SAEs) were reported in ███ of patients, and Grade 3–4 SAEs were reported at a frequency of ███ Drug-related SAEs were reported in ███ of patients, and Grade 3-4 drug-related SAEs were reported at a frequency of ███[82]

B.2.10.1.4 Treatment-related adverse events

██ of patients. The ██A total of ██ ████████████████████████████████[82]The most frequently reported TRAEs (≥10% of patients) by preferred terms (PTs) were fatigue, rash, and diarrhoea (Table 18).

Table 18. CheckMate 142: TRAEs reported in ≥10% of patients[102]

	Any grade (%)	Grade 3-4 (%)	Grade 5 (%)
Total patients with an event	███	███	█
Fatigue*	███	███	█
Rash*	███	███	█
Diarrhoea*	███	███	█
Transaminases increased*	███	███	█
Pruritus*	███	███	█
Hypothyroidism*	███	███	█
Pyrexia*	███	█	█
Hyperthyroidism*	███	█	█
Nausea*	███	███	█
Lipase increased *	███	███	█
Decreased appetite*	███	███	█
Anaemia*	███	███	█

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TRAEs events were assessed during treatment and for up to 30 days after the last dose of study treatment according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).
*Reported in ≥10% of patients.
TRAE: treatment-related adverse event.

B.2.10.1.5 *Adverse events of special interest*

The ██. The most common all-causality AESIs by category were ████████████████████████ and ████████ ██████████████████████ and were manageable using the recommended treatment guidelines for early work-up and intervention.[82] ██████████████████████████ by the investigator. The ██ ████████████████████ (Table 19).[82]

Table 19. CheckMate 142: treatment-related AESIs[82]

	Any grade n (%)	Grade 3-4 n (%)
Treatment-related AESIs		
Skin	████	███
Endocrine	████	███
Gastrointestinal	████	███
Hepatic	████	████
Pulmonary	███	███
Renal	███	███
Hypersensitivity/infusion reactions	███	███
AESI: adverse event of special interest		

Across the AESI categories, the majority of events were manageable using the established algorithms, with resolution occurring when immune-modulating medications (mainly systemic corticosteroids) were administered. ██ ██ ████████████████████████

B.2.10.1.6 *Discontinuation due to adverse events*

All causality AEs leading to discontinuation were reported in ███ of patients (any-grade), and ███ of patients (Grade 3–4). TRAEs leading to discontinuation were reported at a frequency of ███ (any grade) and ███ (Grade 3–4).[82]

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As of the February 2019 DBL, ██████) patients had died. No deaths were attributed to study drug toxicity. The majority of deaths were due to underlying disease progression (████████████████████████████████).[82]

B.2.11. *Ongoing studies*

CheckMate 142 remains ongoing, with an updated database lock expected in ████████.

As a part of its commitment to develop NIVO+IPI in MSI-H/dMMR mCRC, BMS has developed CheckMate 8HW (CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 8HW), an ongoing Phase IIIb, randomised, open-label multi-centre clinical trial of nivolumab monotherapy, NIVO+IPI, or an investigator's choice chemotherapy in patients with MSI-H/dMMR mCRC to confirm the benefit that was observed in CheckMate 142. The chemotherapy arm includes oxaliplatin, folinic acid (leucovorin), fluorouracil, irinotecan, bevacizumab, and cetuximab.[68, 103] Inclusion criteria include histologically confirmed recurrent or metastatic CRC irrespective of prior treatment history, known MSI-H or dMMR status by local testing, and an Eastern Cooperative Oncology Group (ECOG) performance status lower than or equal to 1.[68, 103] The CheckMate 8HW study is ongoing and preliminary results will not be available during this submission process.

The results of CheckMate 8HW will provide comparative efficacy of NIVO+IPI versus the current standard of care in patients with MSI-H/dMRR mCRC who have received at least one prior line of systemic therapy.

B.2.12. *Innovation*

There are a number of first-line treatment options for medically fit patients with MSI-H/dMMR mCRC but these are associated with a high frequency and severity of adverse events. In the second line setting and later, therapeutic options are significantly less effective and may be limited by prior therapy and/or mutational status. A retrospective real-world study in the UK demonstrated that ██ ████████████████████████████████████ over the study period ████████.[55] There remains a significant unmet medical need for efficacious, well tolerated therapeutic options offering meaningful clinical benefit for patients with MSI-H/dMMR mCRC across lines of therapy, and particularly in the previously treated population. The cohort of patients with ████████ included in ██ this ████████████████████████████ demonstrated ████████████████████████████████,[55] suggesting that the level of unmet need may be greater for patients with dMMR/MSI-H mCRC.

No specific guidance has been issued on the management of mCRC in patients who are MSI-H, and no therapies have been assessed by NICE in this patient population.[2, 104, 105] Thus, for the small group of patients with MSI-H mCRC, treatment options are primarily based on evidence obtained from the overall population, which may not be as efficacious in this group,

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particularly in the subgroup of BRAF(+) patients who may have poorer overall survival than patients with BRAF (−) status,[20] as corroborated by UK clinicians.[1]

NIVO+IPI is a highly innovative, targeted immuno-oncology therapy with a unique mechanism of action and published data describing the beneficial impact of therapy in terms of efficacy and safety. As described in B.2.6, NIVO+IPI has significant benefits in terms of patient-relevant outcomes, including high response rates, improved survival (both PFS and OS) and a manageable safety profile. A recent retrospective real-word study, of 49 previously treated patients with dMMR mCRC from 13 UK sites treated with NIVO alone or NIVO+IPI demonstrated significant clinical benefit and acceptable toxicities.[67] Median PFS with NIVO+IPI was 16.7 months, and median OS with NIVO/NIVO+IPI was not reached.[67] This prolonged survival benefit attributed to the unique mode of action of immunotherapy agents, whereby durable responses are observed, can be considered comparable with the long-term survival benefits reported in other cancer indications with longer follow-up including advanced non-small cell lung cancer, renal cell carcinoma and melanoma where a plateau is observed in PFS and OS.[79-81] In previously untreated advanced melanoma, where there is longer follow-up, the NIVO+IPI combination led to greater patient survival after 2 years (64%) than nivolumab or ipilimumab alone (59% and 45%, respectively).[73] This survival benefit is maintained over the long-term, even in the absence of prolonged treatment, as ten-year survival was achieved in 20-25% of melanoma patients after ipilimumab monotherapy administered for four cycles at three-weekly intervals.[106]

Furthermore, NIVO+IPI was associated with clinically significant benefits in quality of life (Section B.2.6.1.8), recently confirmed by UK clinical advisors.[1] In comparison with chemotherapy, NIVO+IPI has improved tolerability, which can potentially help maintain patient dignity and facilitate normal life, as well as enabling patients to spend less time in hospital. Further, as there are few efficacious therapies with a manageable safety profile, NIVO+IPI provides an additional treatment option with proven efficacy and tolerability in patients who may otherwise have been receiving treatments which would manage the patient's symptoms, but with limited impact on survival. Due to its unique mode of action NIVO+IPI is associated with durable responses, increased efficacy, improved tolerability and prolonged survival benefit, all of which improve the patient quality of life. This is consistent with evidence reported across other cancer indications with longer follow-up including advanced non-small cell lung cancer, renal cell carcinoma and melanoma.[79-81]

NIVO+IPI will be the first checkpoint inhibitor immunotherapy to become available for marketing authorisation in Europe for the treatment of dMMR/MSI-H mCRC following prior therapy. The regimen offers the next generation in immuno-oncology treatment, combining the distinct yet complementary mechanism of actions associated with PD-1 (nivolumab) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) (ipilimumab) checkpoint inhibitors. Nivolumab works to restore T-cell activity directed against the tumour to induce an anti-tumour immune response, whilst ipilimumab stimulates the production of active T-cells to continue and increasing the number of activated T-cells surrounding the tumour. NIVO+IPI work synergistically and potentiate the immune-mediated tumour destruction, stimulating the

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patient's own immune system to directly fight cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes. With its innovative mechanism of action, the UK clinical advisors consider NIVO+IPI therapy a "game changer" in the management of MSI-H mCRC.[1]

The lack of immunotherapy treatment options in this indication has recently been identified as a significant unmet need by UK clinical advisors consulted during this submission process, who consider checkpoint inhibitor immunotherapy to be more efficacious, with fewer adverse events than cytotoxic chemotherapy treatments.[1] Clinicians are so confident in the safety and efficacy of immunotherapy treatments in the dMMR/MSI-H mCRC patient group, they seek access to immunotherapies (including nivolumab and ipilimumab) through compassionate use schemes or clinical trial enrolment for their patients in their dMMR MSI-H mCRC patients, which highlights a substantial unmet need for a therapy with proven efficacy and a favourable safety profile in the management of MSI-H mCRC.[1] UK clinical opinion is that NIVO+IPI is a treatment that works for these patients and is completely different to current standard of care. Advisors reported positive experiences with nivolumab in combination with ipilimumab, and nivolumab monotherapy, through individual patient requests at BMS and the Covid interim fund.[1]

The introduction of NIVO+IPI as a highly-innovative and well-tolerated therapy with demonstrable and durable tumour response rates and survival outcomes would change the treatment paradigm for this patient group and represent a 'game-changer' in the management of previously treated dMMR/MSI-H mCRC, according to UK clinical advisors.[1] The adoption of NIVO+IPI by NHS England would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need in the management of this life-threating condition.

B.2.13. *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1. Principal findings from clinical evidence

There are very few therapies with proven efficacy in patients with dMMR/MSI-H mCRC. No therapies have been assessed by NICE in this patient population, and no specific guidance has been issued on the management of mCRC in patients who are MSI-H. Treatment options for this small group of patients are primarily based on evidence that is obtained from the overall population. There are limited treatment options recommended by NICE for patients whose disease has progressed following prior therapy, and even fewer for patients who are more treatment experienced, with poor outcomes. NICE has previously acknowledged that life expectancy is likely to be less than 24 months in this group.[2104, 105] Results of the SLR showed a median OS of 9.48 months.

The clinical evidence supporting use of NIVO+IPI for previously treated dMMR/MSI-H mCRC is primarily derived from CheckMate 142.[83] CheckMate 142 demonstrated that NIVO+IPI was efficacious in terms of response rate

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(███) which translated into lower incidence of progression and extended survival (███████████ ███, indicating vastly longer OS than is available for comparators. Similarly, ███, which greatly exceeds that observed for comparators.[87] CheckMate 142, reporting outcomes from the overall mCRC population, may be considered conservative, as outcomes may be poorer in mCRC patients with MSI-H/dMMR status; a full description of the available evidence is provided in Section B.1.3.2.1.

Previous studies have supported clinical expert opinion that patients with a durable response to immunotherapy can experience long-term survival. A pooled analysis of 1,861 patients with advanced melanoma treated with ipilimumab monotherapy showed a survival curve that began to plateau at 3 years and extended through to at least 10 years.[106] A similar survival pattern has been demonstrated for nivolumab monotherapy in previously-treated advanced renal cell carcinoma, with a 5-year OS rate of 34% in Phase 1/Phase 2 studies.[81] In the Phase 3 trial of NIVO+IPI in advanced melanoma, OS at 5 years was 52% in the NIVO+IPI group, compared with 44% in the nivolumab group, and 26% in the ipilimumab group, suggesting enhanced long-term anti-tumour responses from dual therapy compared to single-checkpoint blockade.[107] In the long-term, patients receiving immunotherapy can experience. a "cure" (i.e. no need for further treatment) and restored quality of life. Moreover, according to UK clinicians, introducing immune checkpoint inhibitor therapy earlier in the treatment pathway, when patients have a better preserved immune system and better prognosis, should result in an even greater long-term clinical benefit.[1]

In the absence of head to head comparisons of NIVO+IPI to relevant comparators, an indirect comparison was conducted using published evidence identified through the SLR. Results derived reported benefits in OS for NIVO+IPI of ███ months, compared with 7.22–17.32 months for comparators. Similarly, mean PFS was ███ months versus 1.83–6.79 months, respectively. Applying MAIC methodology, comparator mean OS ranged from 7.13 months to 17.06 months, while mean PFS ranged from 1.81 months to 6.92 months. The safety profile of NIVO+IPI should also be considered manageable in the context of currently available alternative therapies. In CheckMate 142, Grade 3–4 TRAEs occurred in 32% of patients and were manageable, with meaningful and lasting improvements in key patient-reported outcomes.[83] NHS physicians consulted for this submission confirmed the lower incidence of AEs from immune-oncology treatments compared with cytotoxic chemotherapy regimens. The safety profile of NIVO+IPI in mCRC is consistent with NIVO+IPI across other cancer indications with longer follow-up data including advanced non-small cell lung cancer, renal cell carcinoma and melanoma.[108, 109]

Immune checkpoint inhibitor therapy has the potential to remove the need for further toxic systemic treatment after disease progression following first-line treatments, viewed by clinical advisors as a 'game-changer' in the management of this disease.[1]

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B.2.13.2. Strengths and limitations of the clinical evidence base

B.2.13.2.1 Strengths of study evidence

CheckMate 142 was conducted in line with GCP guidelines, with steps taken to minimise bias and independent monitoring or advisory committees in place to provide oversight of safety and efficacy considerations, study conduct and risk-benefit ratio.

It was primarily designed to assess ORR, OS, and PFS, outcomes of direct relevance to clinical practice. The most important treatment outcomes for patients with dMMR/MSI-H mCRC include survival (PFS and OS), reduced side effects and improved quality of life, and NIVO+IPI provides significant benefits for each of these.

- **Improved survival outcomes:** standard of care for the mCRC overall population are associated with poor outcomes; the weighted mean of reported median OS values was 9.48 months in treatment-experienced patients with mCRC By contrast, clinical trial data presented within this submission demonstrates patients treated with ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮, indicating a substantial survival benefit. This indicates that NIVO+IPI meets the End-of-Life criteria for this indication. Additionally, there are no available therapies with proven efficacy for heavily pre-treated patients with dMMR/MSI-H mCRC, who benefit less from conventional chemotherapy and have a shorter OS than do patients with pMMR mCRC.[22, 23, 31, 38, 40, 41]

- **Improved quality of life**: NIVO+IPI was associated with improvement from baseline in disease-specific patient quality of life (EORTC-QLQ-C30) and a generic health status measure (EQ-5D-3L), demonstrating clinically significant benefits in quality of life using several of the scales.[83]

- **Improved tolerability:** in comparison with currently available treatments, such as chemotherapy, the safety profile for NIVO+IPI can be considered manageable for patients. Further, this safety profile is well-established based on that observed in other indications. UK clinical expert opinion confirmed the improved tolerability of immunotherapy compared with cytotoxic treatments, and reported positive experiences with NIVO+IPI for the treatment of patients with dMMR/MSI-H mCRC.[1]Clinicians confirmed that they offer immunotherapy treatments to this group in preference to chemotherapy options through Patient/Compassionate Access schemes, with successful outcomes.[1]

- **Reduced burden on the NHS**: UK clinical expert opinion concurred that immuno-oncology would reduce burden on NHS services due to both the minimal side effects expected compared with cytotoxic approaches, and the increased efficacy seen in clinical trials. They agreed that whilst chemotherapy treatments improve OS compared to BSC, ultimately the cancer returns which has an ongoing impact on the patient and

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the healthcare system. Conversely, with immuno-oncology a proportion of patients will be cancer free, with no persisting cancer symptoms, allowing treatment cessation typically after a clinically acceptable period of two years. Physicians agreed that a double-immunotherapy approach, such as the use of both nivolumab and ipilimumab would likely be more efficacious than a single immunotherapy treatment alone.

- **Direct evidence for patient population of interest**: The submission presents a non-comparative study evaluating the efficacy of NIVO+IPI in patients with previously treated dMMR/MSI-H mCRC, in line with the patient population in the decision problem. However, as the SLR confirmed, the current evidence base for the comparators of interest is in the overall mCRC population only. Therefore, the evidence base presented within this submission is directly relevant to the patient population in the decision problem, which represents a clear strength of CheckMate 142 opposed to the comparator evidence.

In summary, the strengths of the clinical evidence suggest that the availability of NIVO+IPI would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need.

B.2.13.2.2 *Limitations of clinical evidence base*

The main limitations of the clinical evidence base include the non-comparative study design and use of ORR as primary endpoint. These are outlined fully below. However, these limitations should be viewed within the context of the study strengths and the high unmet need in this patient population.

- **Non-comparative study design:** although CRC is a relatively common cancer,[6, 7] incidence of dMMR/MSI-H CRC is significantly lower (around 15% of early-stage cases,[16-18] and around 4% of metastatic cases regardless of treatment line[21-23]). Based on methods of calculating patient numbers outlined in previous mCRC HTAs,[2] this would equate to around 282 eligible patients in England with dMMR/MSI-H mCRC who had received prior therapy. Because of this low prevalence, clinical trial recruitment of previously treated MSI-H or dMMR mCRC patients is severely limited. A single-arm, non-comparative study design was deemed ethical and relevant to facilitate a rapid assessment and confirmation of clinical activity in a population with very poor prognosis and few therapies with proven efficacy. As outlined in Section B.2.11, CheckMate 8HW will provide comparative efficacy of NIVO+IPI versus the current standard of care in patients with MSI-H/dMRR mCRC who have received at least one prior line of systemic therapy, however, preliminary results won't be available during this submission process. Due to the immediate and urgent unmet need and lack of effective treatments in this patient population, many lives would be lost if NIVO+IPI would not be made available for patients while awaiting CheckMate 8HW trial results, which would be deemed unethical.

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- **Use of ORR as primary endpoint:** although there are advantages to the use of ORR as primary endpoint in CheckMate 142, such as it allows earlier assessment with a smaller sample size compared with survival studies, it can show the effect of the drug(s) on the tumour, and it is generally based on objective and quantitative assessment,[110] there are also disadvantages. For instance, definitions may vary across studies, it may require frequent assessment, and it may not correlate with survival.[110] In CheckMate 142, the use of the ORR allowed the ongoing evaluation of response at different data cuts. ██ ██.[87] It should be noted that PFS and OS are considered independent of patients and/or clinicians (particularly OS), which limits the opportunity for assessment bias. The efficacy of NIVO+IPI is such that in terms of survival benefit, median OS has yet to be reached.

B.2.13.3. Relevance of the evidence base to the decision problem

The submission presents a non-comparative study evaluating the efficacy of NIVO+IPI in patients with previously treated dMMR/MSI-H mCRC, in line with the decision problem. Further, a number of indirect comparisons applying different methodologies versus alternative comparators are presented in order to provide evidence of comparative effectiveness. In addition, outcomes considered are in line with the decision problem set out by NICE.

Thus, it can be considered that the evidence base presented within this submission is directly relevant to the decision problem and is the best available evidence.

B.2.13.4. External validity of study results to patients in routine clinical practice

In terms of baseline characteristics, patients enrolled in CheckMate 142 can be considered broadly representative of the UK dMMR/MSI-H mCRC population, with subgroups provided for analysis where possible.

It should be noted that enrolment into CheckMate 142 required previous treatment with a fluoropyrimidine-based therapy and the anticipated indication is ███ ██ which closely reflects the current treatment pathway as recommended by NICE.

It is acknowledged that over half of patients in the CheckMate 142 overall population (57.0%) had previously received a VEGF inhibitor,[83] which is not a recommended treatment option in the UK.[60] However, there is no evidence to suggest that NIVO+IPI would be less efficacious in patients who had not received these therapies. While patients who are more heavily pre-treated are more likely to be resistant to subsequent therapy,[35] the response rate during

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CheckMate 142 remained consistent between patient subgroups, including subgroups based on number of prior therapies, as described in Section B.2.7.

The majority of patients in CheckMate 142 were <65 years of age (68%),[83] in contrast to clinical practice where the majority of patients at >65 years of age[7]. However, this was not corroborated by UK clinical expert opinion, which confirmed that patients with dMMR/MSI-H mCRC tend to be younger in UK clinical practice. This is supported by a UK real-world evidence study, detailed in Section B.2.13.4.1. Further, patients with Lynch syndrome typically develop cancers at a younger age, making the results more relevant to the UK. Despite this, as detailed in Section B.2.7, NIVO+IPI is equally efficacious in older patients (████████████████████████████████).[87]

Further, it is noted that patients enrolled into CheckMate 142 had ECOG status 0–1, which is markedly improved versus the performance status of patients in UK clinical practice. However, this is common across clinical studies for cancer studies, particularly in therapeutic areas where intensive combination regimens may be used or where patients may decline rapidly. This can be observed from the performance status extracted from comparable studies in the previously treated mCRC population, as described in Appendix D, where all studies focused on patients who were relatively fit.

The ITC results are limited by the fact that none of the SLR-identified studies enrolled entirely dMMR/MSI-H mCRC patients or reported outcomes in this patient population. By contrast, CheckMate 142 required MSI-H status for enrolment into the NIVO+IPI arm. As such, this baseline characteristic cannot be adjusted for when undertaking a MAIC. As previously discussed, response to chemotherapeutics may not be equivalent between MSI-H and MSS tumours when the disease has progressed to an advanced stage.[24, 43] Available evidence suggests patients with dMMR/MSI-H mCRC benefit less from conventional chemotherapy and experience a shorter OS than pMMR mCRC patients.[22, 23, 31, 38, 40, 41] UK clinical expert opinion also indicated that patients with dMMR/MSI-H CRC that has progressed to the metastatic stage experience very poor outcomes which are worse than those of the overall metastatic population.[1]

B.2.13.4.1 UK real-world evidence supporting NIVO+IPI use

A recently published retrospective analysis assessed use of NIVO monotherapy or NIVO+IPI in 49 UK patients (NIVO: 37 patients; NIVO+IPI: 12 patients), provided as part of the UK BMS Individual Patient Supply Request programme.[67] All 49 patients had MSI-H/dMMR mCRC with the exception of two patients with small bowel adenocarcinomas and one patient with appendiceal adenocarcinoma. Median age was 57 years (range: 22-88 years), 55.1% were female, 59.2% had right-sided tumours and 26.5% had BRAF mutations. The majority of patients had ECOG performance status score of 1 (51.0%), but 4 patients (8.2%) had a performance score of 2. Of these patients, 18 received second-line therapy, 10 received third-line therapy and 9 received fourth-line therapy; the remaining 9 patients received adjuvant therapy.[67]

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Median follow-up from start of treatment was 17.7 months (8.1–30.0 months) and median OS was not reached. Median PFS was 10.8 months in the overall population, 8.3 months in the NIVO population and 16.7 months in the NIVO+IPI population. Further, outcomes appeared consistent across treatment lines, as demonstrated in Figure 22.[67]

Figure 22. UK real-world evidence for NIVO monotherapy and NIVO+IPI (A: overall population; B: stratified by performance score; C: stratified by treatment line; D stratified by regimen)[67]
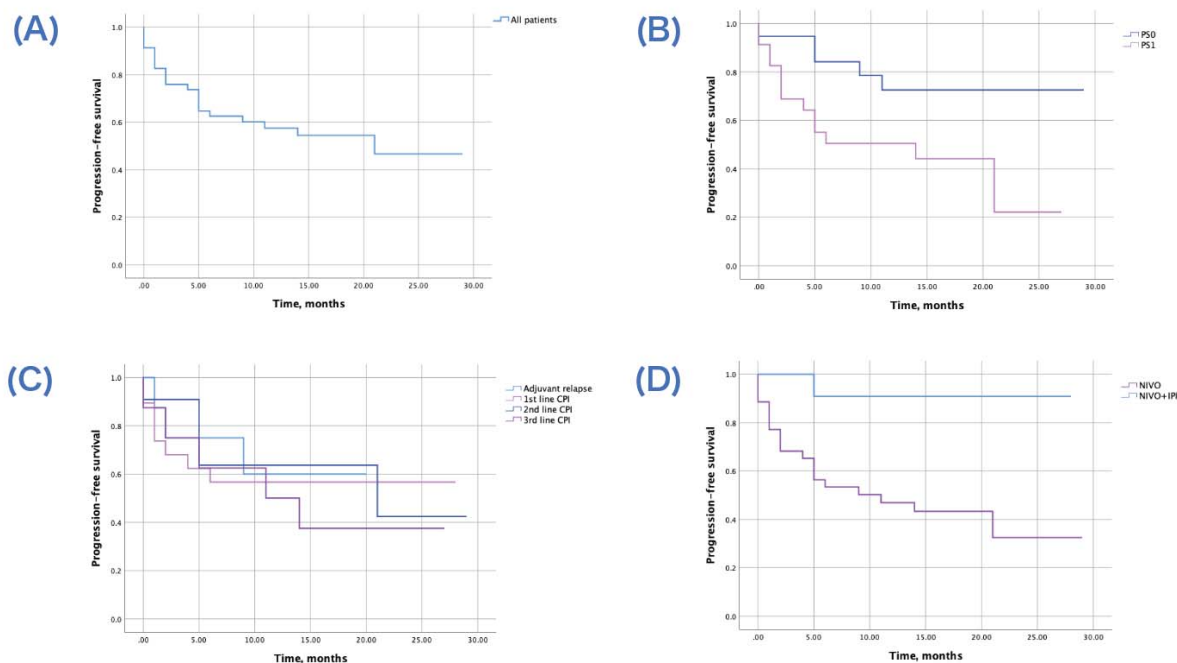
B.2.13.5. Application of NICE end-of-life criteria to NIVO+IPI use in dMMR/MSI-H CRC following prior therapy

Application of NICE end-of-life criteria to NIVO+IPI use in the ███ should be set in the context of the low patient numbers and the very high unmet need. Prevalence of MSI-H is dependent on disease stage, comprising around 15% of early stage CRC,[16-18] but only around 4% of patients with metastatic disease. [21-23] These estimates are supported by UK clinical expert opinion, which suggests that the subgroup of dMMR/MSI-H mCRC patients is very small particularly when taking into account the anticipated indication. Based on methods of calculating patient numbers outlined in previous HTAs and taking into account the proposed indication, this would equate to around 282 patients in the UK eligible for treatment with NIVO+IPI for dMMR/MSI-H mCRC, in line with the anticipated marketing authorisation indication.

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The current standard of care for the overall mCRC population is associated with poor outcomes and estimates of median OS in pre-treated patients extended to 9.48 months (Section B.2.9.1). Previous NICE appraisals in this patient population have noted that life expectancy is likely to be less than 24 months, which was supported during consultation with clinicians for this submission[2, 104, 105] The very poor prognosis for this patient group and lack of effective and tolerable dMMR/MSI-H-specific treatments highlights the high degree of unmet medical need in this patient population.

NIVO+IPI has a one-year OS rate of 84.9%, which is significantly higher than for comparators (weighted mean of reported values: 34.91%; range: 0-69.5%).[83] The weighted mean of reported values was 9.48 months for median OS (with weighted mean median OS ranging from 6.05-12.73 months for comparators), while median OS for NIVO+IPI was not reached despite ████████████████████. Additionally, based on the ITC presented in Section B.2.9.2 the estimated mean OS for NIVO+IPI is around ████████, while comparator mean OS ranged from 7.22 months to 20.41 months. A comparison of CheckMate 142 with outcomes from the overall mCRC population may be considered conservative, as outcomes may be poorer in mCRC patients with MSI-H/dMMR status, as described in Section B.1.3.2.1. However, despite comparing to an overall population, expectation is that the benefit will still exceed 3 months.

The case for application of NICE end-of-life criteria is set out in Table 20, and based on this evidence, it can be considered that NIVO+IPI meets both criteria for end-of-life.

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Table 20. End-of-life criteria

Criterion	Data available	Reference in submission
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Current SoC for the mCRC overall population is associated with poor outcomes. Based on SLR-identified studies, the weighted mean of reported values was 9.48 months for median OS, while median OS for NIVO+IPI was not reached despite median follow-up of ▉▉▉▉▉. Similarly, weighted mean of reported values was 36.33% for OS at one year, compared with 85% for NIVO+IPI. Mean OS for comparators was derived from the ITC and ranged from 7.22–20.41 months. This figure is supported by previous NICE appraisals in this patient population (including the TA405 appraisal) which have accepted that life expectancy is likely to be less than 24 months. [2, 104, 105]	Section B.2.6.1.2 <u>B.2.9</u>
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉ so that extrapolation is required to provide evidence of mean/median OS. However, this is in itself evidence of at least 3 months of benefit, given median OS outcomes in the overall mCRC population (weighted mean of SLR-reported median OS values: 6.05-12.73 months). Based on the ITC presented in Section B.2.9., NIVO+IPI appears to have a mean incremental OS benefit over all the comparators of interest in the unadjusted and adjusted ITC (▉▉▉▉▉versus 7.22-17.32 months unadjusted and 7.55 – 20.41 months adjusted). It should be noted that the mean incremental benefit should be considered as the most appropriate summary statistic when assessing applicability of end of life criteria. In support of this benefit, OS at was 84.9% and ▉▉▉▉ at one and two years, respectively, in the CheckMate 142 population, compared with 0-69.5% OS at one year for comparators, indicating substantially greater median OS for NIVO+IPI treated patients compared with SoC.	Section B.2.6.1.2 B.2.9
ITC: indirect treatment comparison; mCRC: metastatic colorectal cancer; OS: overall survival; SLR: systematic literature review; SoC: standard of care.		

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B.3. Cost-effectiveness

Base case analysis

- Use of NIVO+IPI results in an increased mean OS ranging from ▉ years (versus raltitrexed) to ▉ years (versus BSC), as well as additional discounted QALYs and life years of up to ▉ and ▉, respectively.

- Discounted incremental costs were estimated to be ▉▉▉–▉▉▉ under base case assumptions and the resultant ICERs were £13,367-£15,346 per QALY, which are considered to be cost-effective at a willingness-to-pay threshold of £50,000 per QALY.

Sensitivity analysis

- In the probabilistic sensitivity analysis and deterministic sensitivity analysis, NIVO+IPI was cost-effective in all scenarios at a willingness-to-pay threshold of £50,000 per QALY.

- Extensive scenario analyses were undertaken, reflecting the assumptions required to undertake plausible, robust and transparent base case analysis. Within these scenario analyses, all of the ICERs remain below the £50,000 per QALY threshold

B.3.1. Published cost-effectiveness studies

In line with the NICE Guide to the methods of technology appraisal 2013[111], an SLR was conducted to identify cost-effectiveness studies for the treatment of mCRC. In brief, electronic database searches (MEDLINE, Embase, the Cochrane library and EconLit) were conducted in January 2017, and subsequently updated in August 2020 (Figure 23). Publications describing full economic evaluations of interventions aimed at managing mCRC were included. Full details of the process and methods to identify and select the relevant cost-effectiveness evidence are summarised in Appendix G.

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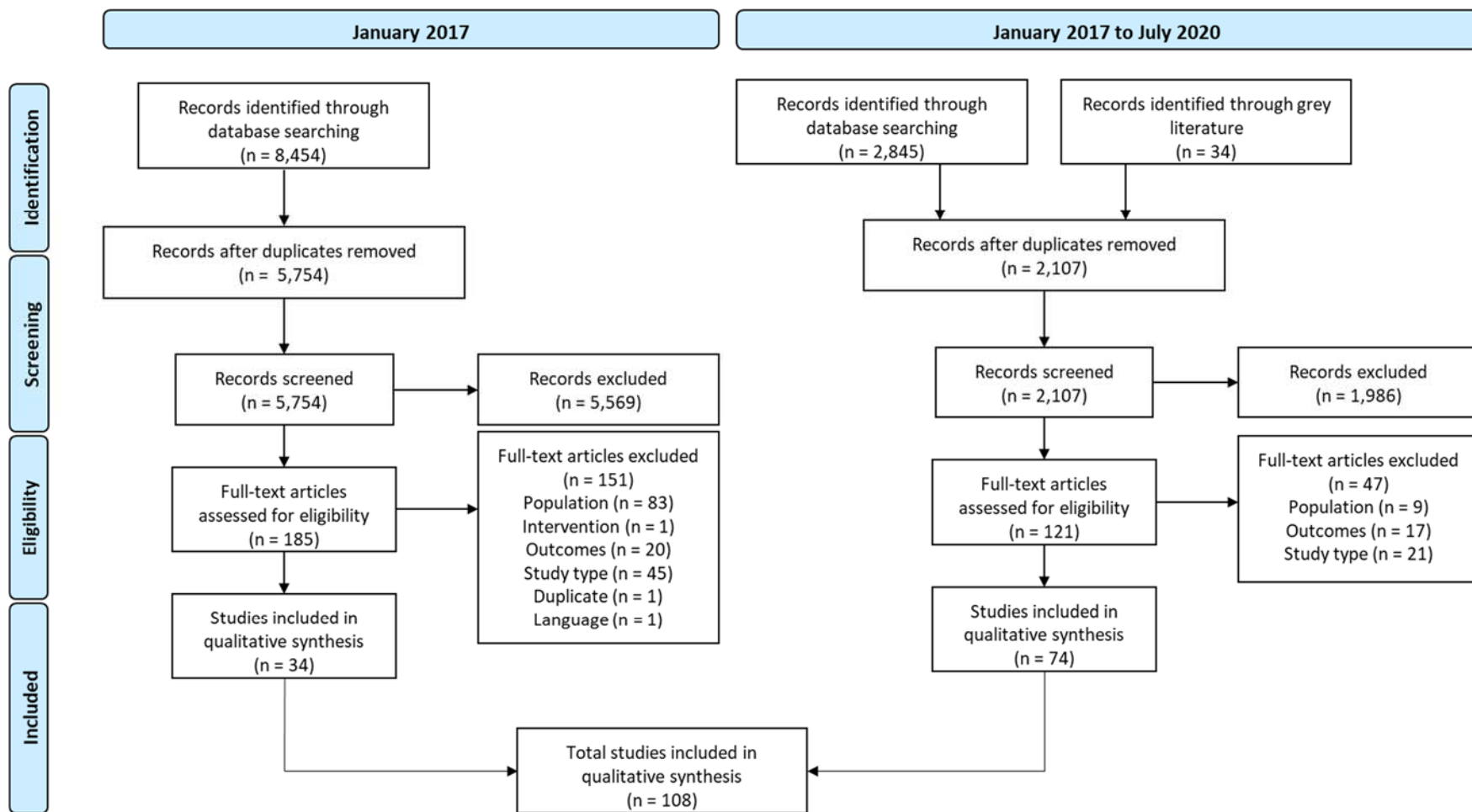
Figure 23. PRISMA diagram illustrating the study selection process for identifying cost-effectiveness studies for the period from database inception to August 2020

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B.3.2. *Economic analysis*

The economic case presented in this submission is based on a conventional cost-utility analysis, assessing use of NIVO+IPI versus comparators for the ███ ███, taking into account a simple discount patient access scheme (PAS) for NIVO+IPI.

A partitioned survival model structure has been utilised. The economic modelling of NIVO+IPI and the comparator in this particular indication does not require extensive complexity with regard to subsequent lines of treatment or time-dependency of model inputs, which may necessitate use of a Markov model. Further, a partitioned survival model may replicate survival outcomes with a higher degree of accuracy compared with a Markov model; however, it is noted that differences in outcomes should be minimal, particularly where appropriate transition rates have been derived.[101]

The model utilises three health states (pre-progression, post-progression and death) to reflect disease progression, and the subsequent cost and utility consequences of different health states; in line with clinical practice, patients may receive treatment beyond progression. The model structure has been chosen to reflect the most important treatment outcomes for most dMMR/MSI-H mCRC patients: survival (progression free and overall), side effects, symptom control and quality of life. Survival curves have been applied to estimate PFS and OS in each treatment arm, while health state utilities and costs have been applied to reflect the symptom control and quality of life experienced by patients receiving NIVO+IPI or comparators. Treatment-specific AE probabilities, alongside AE event-specific costs, are used to estimate the incidence and economic consequences associated with treatment-related AEs (Section B.3.3.3.2).

Of note, the structure of the partitioned survival model accommodates treatment discontinuation, use of initial therapy beyond progression and subsequent lines of therapy. This is of importance in the appraisal of NIVO+IPI, where therapies may be continued beyond progression, subject to a stopping rule or discontinued upon disease progression.

B.3.2.1. Description of analyses

Within this submission, efficacy for NIVO+IPI has been derived from CheckMate 142, while efficacy for comparators has been derived from the MAIC described in Section B.2.9. The limitations of this comparison have been described previously, however; this can be considered the best available evidence to inform decision making for NIVO+IPI versus relevant comparators.

All analyses within this submission have been conducted from the payer perspective, in this case the NHS. Key assumptions were validated by medical/clinical oncologists specialising in

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gastric cancers. The methods related to the economic methodology were based on the most recent NICE reference case.

B.3.2.2. Patient population

The economic evaluation considers the use of nivolumab in combination with ipilimumab for the

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██, in line with the anticipated licensed indication.

As noted in Section B.1.3.3, there is limited guidance on the treatment options for patients with dMMR/MSI-H mCRC patients in the UK. However, clinical opinion has stated that dMMR/MSI-H patients are treated similarly to the overall mCRC population. In UK clinical practice, NICE guidance and clinical expert opinion suggest that mCRC patients will predominantly receive either FOLFOX or FOLFIRI in the previously treated setting, while trifluridine-tipiracil and BSC are treatment options for patients in later lines. According to clinical expert opinion, single agent irinotecan and raltitrexed are rarely used in UK clinical practice. Assessment versus these two comparators have been provided in the submission for completeness with the final scope, however, it is recommended that it should not inform decision making.

In the base case analysis, baseline patient parameters are derived from the baseline characteristics of patients enrolled into the CheckMate 142 study, as detailed in Table 21. Sensitivity analyses will be undertaken to assess the impact of alternative baseline patient parameters.

Table 21. Baseline patient parameters

Parameter	Mean	SE	Source
Baseline age (years)	56.60	1.26	Eligible population from CheckMate 142[83]
Proportion of cohort male	58.8%	4.5%	
Cohort size	1,000	-	Assumption
SE: standard error			

B.3.2.3. Model structure

A de novo partitioned survival model was developed, applying health states representing pre-progression, post-progression and death (Figure 24). Unlike a Markov model, the number of people in any state at successive points in time is not dictated by transition probabilities. Instead, the model estimates the proportion of a cohort in each state based upon parametric or semi-parametric survival equations. These health states reflect disease severity and determine use of healthcare resources, health-related quality of life and mortality rates. To reflect the nature of dMMR/MSI-H mCRC and available evidence, the model assumes that dMMR/MSI-H mCRC phases are consecutive, which means patients are not able to revert to pre-progression from more advanced phases of the disease. Although patients may be able

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to respond to therapy following progression, patients are still considered to have a higher hazard and an increased resource use. As evidence for this, the heavily pre-treated patients in the RECOURSE study were still able to achieve a complete or partial response, but OS remained low. Hence, this assumption can be considered appropriate.

Using a weekly cycle length, the model predicts the proportion of the population who experience a progression or death event. Weekly cycles were considered appropriate for this evaluation because it enables the model to reflect the timings of drug administrations associated with both NIVO+IPI and comparator therapies. Weekly cycles further capture a realistic minimum time during which the symptoms or responses can change in UK clinical practice.
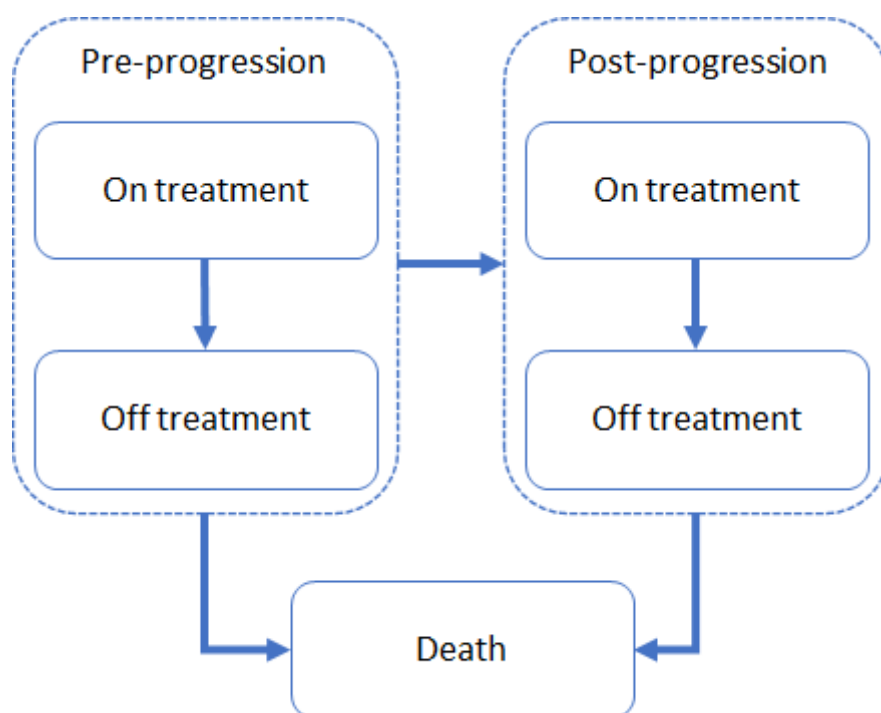
Figure 24. Conceptual model schematic

B.3.2.3.1 Derivation of health state occupancy estimates

Health state occupancy is defined by treatment specific PFS and OS extrapolations, derived from available data (as described in Section B.3.3.2). An overview of model implementation of survival curves is presented in Figure 25.

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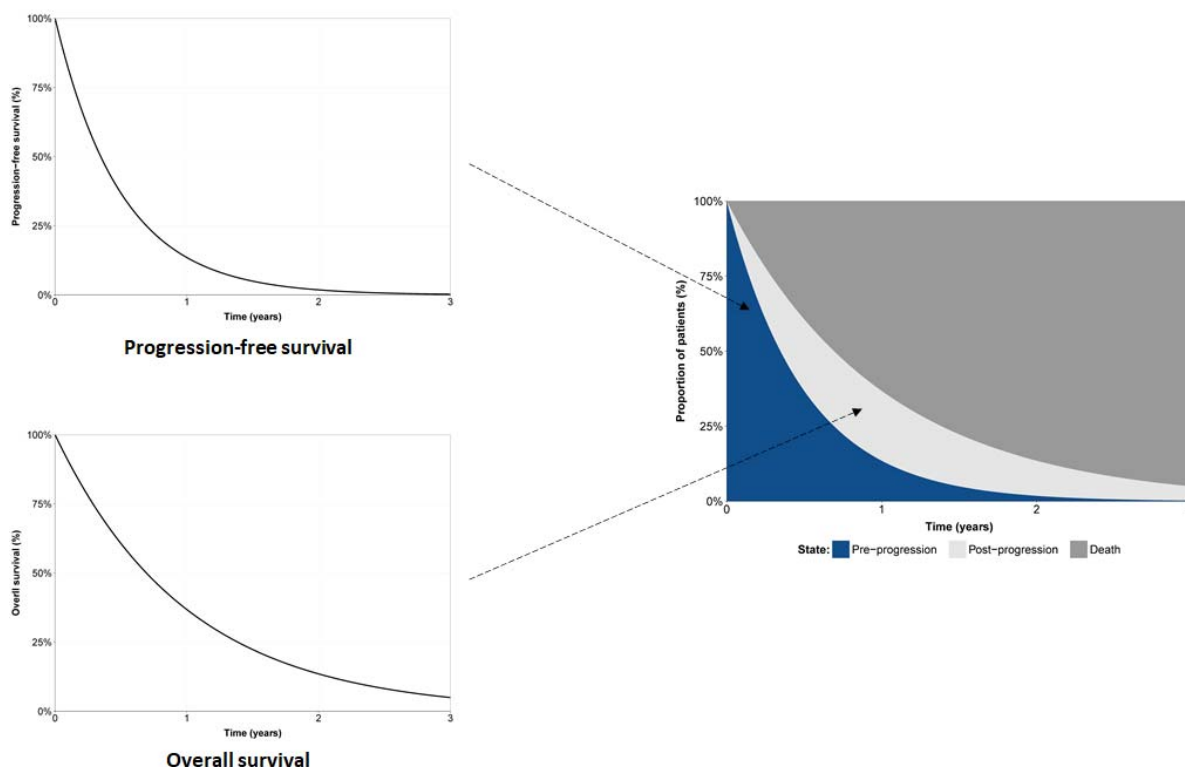
Figure 25. Overview of survival curve implementation in the model

As these PFS and OS data implicitly include the effects of any subsequent treatment that may have been administered, the need to explicitly incorporate the survival effects of these subsequent treatments is negated.

For NIVO+IPI, parametric curves for PFS and OS were fitted using patient-level data from the relevant patient cohort in CheckMate 142; methods for deriving these curves are provided in Section B.3.3.2. Data for relevant comparators is derived from the SLR and ITCs described in Section B.2.9.2. These ITCs provide a measure of relative mean survival for comparators versus the NIVO+IPI cohort, which is then applied against the NIVO+IPI cohort to derive a mean survival for the comparator.

Comparator survival is derived from the MAIC described in Section B.2.9.2, which provides mean survival estimates for each comparator of interest. In the absence of other information to inform the shape of these extrapolations, constant hazards (i.e. exponential parametric functions) were assumed, as described in Section B.2.9.2.2. It should be noted that this does not impact on outcomes, as mean survival remains as per the MAIC output, regardless of the extrapolation chosen.

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B.3.2.3.2 *Derivation of treatment line occupancy*

Patients enter the model following failure of prior therapies and can receive NIVO+IPI or a comparator treatment. Following treatment cessation or progression, patients receive a final line of therapy, as detailed in Section B.3.5.1.4. As a simplifying assumption, it is assumed that patients may not discontinue this final line of therapy and therefore remain on this until death or the end of the modelled time horizon.

In the base case analysis, the proportion of patients on initial or subsequent treatment lines is based on the following criteria:
- Observed time on treatment data
- Treatment cessation (where treatment duration is specified, for example in set treatment durations or stopping rules)

B.3.2.3.3 *Treatment sequences*

Patients enter the model following failure of prior therapies and can receive NIVO+IPI or a comparator treatment. Following treatment discontinuation, patients in both arms can receive subsequent therapy, described in Section B.3.5.1.4. Following treatment cessation or progression, patients can receive a subsequent therapy (comprising of a one-off cost on the first cycle), which is based on those specified during TA405,[2] as detailed in Section B.3.5.1.4; however, as a simplifying assumption, it is assumed that patients may not discontinue this final line of therapy, as it is assumed to include palliative care.

B.3.2.3.4 *Outcome measures*

The primary model output is the incremental cost-effectiveness ratio (ICER) expressed as incremental costs per QALY gained. Additionally, the model provides an overview of other outcomes, such as LYs gained, and clinically relevant outcomes, such as predicted median OS and PFS.

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Table 22. Features of the economic analysis

Factor	Previous appraisals			Current appraisal	
	TA405 (Trifluridine-tipiracil)	TA307 (Aflibercept)	TA242	Chosen values	Justification
Time horizon	10 years.	15 years	10 years	Lifetime (up to 50 years or 2,609 weeks).	This is in line with the NICE reference[111] and ensures that all events have occurred, and all patients are accounted for. However, a shorter time horizon is assessed in sensitivity analysis.
Treatment waning effect	None.	None	None	None.	This is in line with a previous NICE appraisal.[2]
Source of utilities	Weighted utilities from the NICE submission for cetuximab (metastatic CRC 1st line) and the CORRECT study (regorafenib previously treated metastatic CRC).	An observational, non-interventional, cross-sectional study (mCRC utilities study) was performed by Sanofi (redacted)	Utility data obtained in the CO.17 trial, a phase III randomised, open-label study in patients with pre-treated metastatic EGFR-positive CRC	CheckMate 142 utility data is used to inform on treatment utility, with TA242[104] informing off treatment utility (assumed to be equal to post-progression utility).	CheckMate 142 collected utility data using the EQ-5D-3L. In line with the NICE reference case, trial utilities collected as part of CheckMate 142 (baseline and every 6 weeks until the end of the treatment phase and subsequently ever 12 weeks during the follow-up phase) have been applied in the base case analysis for patients receiving NIVO+IPI for an on treatment utility. Given the lack of trial data for off treatment utilities, off treatment utility is in line with TA242 for both treatment arms.[104]
Source of costs	Health state resource use stratified by progression status and active treatment versus BSC (including oral chemotherapy day case attendance; medical oncology outpatient consultation, GP home consultation, community nurse specialist visit, home health visitor, district nurse visit, GP surgery visit).	Resource use informed by retrospective observational study (academic in confidence, so not available) Cost of subsequent therapies following initial treatment derived from VELOUR study (academic in confidence, so not available)	Costs of the interventions and comparators included KRAS testing, drug acquisition, drug administration, consultant outpatient visits, CT scans, and BSC in progressed disease. Costs of treating adverse events were based on the CO.17 trial.	As per TA405.[2]	Costs of intervention and comparators included drug acquisition, administration and monitoring costs and costs of tests. Costs of available generic comparators were sourced from the Monthly Index of Medical Specialities (MIMS). Costs of BSC were identified from a previous NICE appraisal.[2] Further costs consisted of follow-up, adverse event, hospitalisation, third-line therapy (drug costs, administration and follow-up care), terminal care costs and adverse events.

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B.3.2.4. Intervention technology and comparators

Based on available NICE guidance in the mCRC population, the final scope and clinical opinion, the following comparators were deemed most appropriate for the ██

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- FOLFIRI: 5-FU, folinic acid and irinotecan
- FOLFOX: 5-FU, folinic acid and oxaliplatin
- Trifluridine/tipiracil
- BSC

To note, clinical expert opinion confirmed that both single agent irinotecan and raltitrexed are rarely used in clinical practice (<5% patients), and mainly in patients where other treatments are contraindicated. Hence, FOLFIRI, FOLFOX, trifluridine/tipiracil and BSC can be considered primary comparators. Comparisons to single agent irinotecan and raltitrexed have been provided as they were listed in the final scope, however, their limited use in clinical practice means these assessments are unlikely useful for decision making.

B.3.3. *Clinical parameters and variables*

B.3.3.1. Evidence synthesis

As discussed in Section B.2, evidence to describe the efficacy of NIVO+IPI for the treatment of previously treated MSI-H mCRC is primarily derived from CheckMate 142, a non-comparative Phase II study evaluating nivolumab as monotherapy, in combination with ipilimumab, or in combination with other agents, for the treatment of metastatic MSI-H CRC. The efficacy of NIVO+IPI was derived from the cStage arm of the study (see section B.2.3.1).

In order to provide comparative efficacy data for NIVO+IPI versus all relevant comparator treatments, a series of ITC analyses were undertaken, including:

- A MAIC using available covariates correlated with outcome, determined by multivariate analysis of CheckMate 142 data for OS and PFS (a subset of: region – Europe, age, sex, race, KRAS mutation, ECOG PS, time from diagnosis to first dose, primary tumour location – rectum, one prior systemic therapy in metastatic setting).

- A pooled set of outcomes: based on the weighted mean of outcomes reported in the SLR. In this analysis, survival outcomes are derived from reported median survival data, and do not include outcomes derived from survival at time points or Kaplan-Meier data. Further, these outcomes are not combined based on relative measures versus CheckMate 142 but are instead simply weighted by study size. This limits the number of calculations, assumptions and inferences required to provide comparisons. Pooling

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of this wide set of available data demonstrated consistency of outcomes between the SLR and MAIC.

- An unadjusted analysis applying evidence from one study for each comparator. These survival outcomes include data derived from Kaplan-Meier data, median survival and survival at outcomes, with survival outcomes digitised and extrapolated using parametric models selected from a range of candidate models fitted to the digitised data considerate of goodness of fit and clinical plausibility.

It is acknowledged that these analyses have inherent limitations, not least with regard to the applicability of the patient population from the published literature to the decision problem. Despite this, the MAIC outcomes can be considered the best available evidence for the comparators. This comparison is not expected to favour CheckMate 142, which measured outcomes in an MSI-H specific population, who are expected to have worse prognosis under comparative therapies. The MAIC data set is used to derive comparator efficacy in the base case analysis; all alternative clinical inputs are assessed through scenario analysis.

B.3.3.2. Parameterisation of overall survival and progression-free survival

B.3.3.2.1 Nivolumab plus ipilimumab

Clinical data to inform NIVO+IPI PFS and OS can be derived from CheckMate 142. However, follow-up was substantially less than the maximum time horizon of the model. Therefore, parametric extrapolation of survival data from the study was required to inform long-term outcomes, undertaken with reference to the guidance from the NICE Decision Support Unit (DSU)[112] and Bagust and Beale (2014)[113] within the context of only using single-arm data.

A full description of methods used to undertake parametric extrapolation is provided in Appendix M. In brief, parametric functions that inform survival curves were developed using patient-level data from the NIVO+IPI treatment arm of CheckMate 142 based on the February 2019 database lock.

Progression events were based on investigator-assessed outcomes from CheckMate 142 and were defined as in this study. Death events from CheckMate 142 were used to inform OS modelling. Parametric survival functions were fitted to the extracted data using the R statistics environment, including exponential, Weibull, log-logistic, lognormal, Gompertz and generalised-gamma survival distributions. Additionally, spline models were considered, as well as semi-parametric models assessing the impact of different split points and subsequent parametric functions, in line with the approach taken in recent appraisals of immuno-oncology agents.[114, 115]

Goodness-of-fit was evaluated using the Akaike and Bayesian Information Criteria (AIC and BIC, respectively); minimisation of these measures is used to indicate goodness-of-fit whilst penalising overfitting, so that a smaller value demonstrates a more appropriate fit. In addition

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to assessment of goodness-of-fit statistics, the appropriateness of the parametric extrapolation was by visual inspection of the fit over the observed period and consideration of the log cumulative hazard plots.

It is worth noting that while the above methods for validating the extrapolation of progression and death events are appropriate, they are also necessarily constrained by derivation from observed data, which is, as previously indicated, limited by the availability of follow-up data. Therefore, the plausibility of the extrapolation was assessed through consideration of the long-term hazard profile and the extrapolated mean survival estimates. Additionally, clinical expert opinion was sought to ensure that the survival extrapolation approach can be considered appropriate.

Kaplan-Meier plots describing PFS and OS in the NIVO+IPI arm demonstrate a high initial hazard, particularly for PFS, with a significant number of events occurring immediately after study entry, perhaps reflecting the poor prognosis in this patient population. This was followed by a lower hazard in the longer-term in both study arms. Parametric models didn't adequately reflect this change in hazard, particularly for PFS. Hence, a semi-parametric approach was considered appropriate as it reflected the high initial hazard but applied the maximum amount of data to inform the long-term extrapolation.

Applying Kaplan-Meier data until 6.44 months followed by parametric extrapolation enabled the initial hazard to be modelled appropriately and captured the high rate of events between study entry and six months. Switching to parametric extrapolation from 6.44 months used the maximum number of events to inform long-term extrapolation and describe the lower long-term hazard. This semi-parametric approach was applied for both PFS and OS.

In order to model PFS for NIVO+IPI, Kaplan-Meier data was applied until 6.44 months followed by parametric extrapolation using the exponential distribution to provide an appropriate fit. Similarly, a semi-parametric approach was used for modelling OS, where Kaplan-Meier data was applied until 6.44 months followed by parametric extrapolation using the log-logistic distribution. These approaches were deemed appropriate as it provided an adequate fit to the data.

A full description of methods used to undertake parametric extrapolation is provided in Appendix M. A summary of survival outcomes following extrapolation is provided in Table 23.

B.3.3.2.1.1. Progression-free survival

Standard parametric functions were assessed, as outlined in Appendix M. However, only the generalised gamma was capable of approximating the survival function. Even in this case, the observed fit to the early data was poor, and given the expectation of heterogeneity of response to immuno-oncology therapies, alternative models capable of representing this population heterogeneity were sought.

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By contrast, models fitted from 6.44 months, as presented in Figure 26, did not deviate substantially from the data and provided a relatively close range of survival extrapolations. Given that the exponential function provided the best goodness of fit statistics in terms of AIC and BIC, as well as a close fit to the data, this function was applied in the base case analysis. However, it is acknowledged that the log-logistic provided a similarly close fit, with comparable long-term extrapolation and fits with hazard progression observed for immune-oncology therapies in other indications. Hence, use of the exponential function can be considered conservative.

B.3.3.2.1.2. Overall survival

Of the standard statistical models assessed, only the Gompertz gave a satisfactory fit, as outlined in Appendix M. Whilst this model form was consistent with the available data, the statistic model implicitly included an assumption of zero excess hazard through a long period of extrapolation, and so alternative models were sought.

Models fitted from 6.44 months, as presented in Figure 27, demonstrated similar characteristics, with the exception of the exponential model, which demonstrated a noticeably poor fit to the data, in line with the observation that a constant hazard profile is incapable of representing well the monotonically decreasing hazard in this portion of the data. Similarly, the Gompertz was excluded from assessment; although goodness-of-fit statistics were excellent, the model again predicted zero excess hazard in the long-term extrapolation, which may be implausible. After excluding these models, the log-logistic was applied in the base case analysis due to its goodness-of-fit statistics and the maintenance of excess hazard into extrapolation. However, it should be noted that less conservative models provided similar fits to the observed data, with similar AIC/BIC statistics.

Table 23. Extrapolation of survival outcomes from CheckMate 142 NIVO+IPI

	PFS	OS
Extrapolation method	Semi-parametric: Kaplan-Meier to 6.44 months Exponential fitting	Semi-parametric: Kaplan-Meier to 6.44 months Log-logistic fitting

Figure 26. CheckMate 142 NIVO+IPI investigator-assessed progression-free survival extrapolation

Figure 27. CheckMate 142 NIVO+IPI overall survival extrapolation

B.3.3.2.1.3. Clinical rationale and validation of survival extrapolation

Clinicians were consulted regarding their opinion upon the long-term survival and progression-free survival of patients in this subgroup receiving treatment with NIVO+IPI.[1] In these discussions, clinicians expressed an expectation that a large proportion of patients without progression at 2 years would be surviving at 5 years, and that durable response may be expected to continue for an indefinite period, with no evidence to suggest that this would be

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less than 5 years, especially in a young population with few comorbidities and lower risk of immune-related AEs.

The selected extrapolation for OS maintains an excess hazard of death due to disease at all times, but as a log-logistic model, this decreases to a minimal value above matched general population mortality in the long term. Other models decrease at a faster rate, with the Gompertz achieving statistical cure; however, due to the relative immaturity of the survival data, and the presence of patients alive and in post-progression at the end of follow-up, the statistical cure rate implied by this model was considered to be optimistic.

The selected extrapolation for PFS maintains a constant hazard through extrapolation, due to unclear signals within the data regarding hazard progression. Per clinical expert advice, a decreasing hazard is expected, but models suited for providing this profile did not in general provide long-term decreasing hazard when fitted to the trial data. The exponential model is thus considered conservative per expert advice but respects the primacy of the observed trial data.

Sensitivity analyses were performed using a variety of plausible models for each outcome.

B.3.3.2.1.4. Validation of survival curves applied in the economic evaluation

There are no other studies with which to validate the results for extrapolation of the NIVO+IPI arm other than the informing trial, CheckMate-142. The extrapolated curves and approaches were compared to the observed values as much as possible. This method informed selection of the most appropriate modelling approach and fit as a form of validation. The results for PFS and OS can be seen in Table 24 and Table 25, respectively.

Overall, the semi-parametric models show less overall variation in the estimates and are closer to the observed values than the parametric models. This is particularly important with reference to the median values as there are more events initially and these incur cost which need to be well represented in cost-effectiveness analysis.

Further, the identified extrapolations provide a plausible combined model of NIVO+IPI in the treatment of MSI-H/dMMR mCRC. As depicted in Figure 28, PFS and time on treatment do not approach the Kaplan-Meier data or extrapolations for OS. By contrast, PFS and time on treatment show two overlap periods, where patients may continue treatment beyond progression or may discontinue treatment ahead of progression.

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Table 24. Observed and predicted estimates of progression-free survival

Distribution	Observed	Parametric	Semi-parametric	Observed	Parametric	Semi-parametric	Observed	Parametric	Semi-parametric
	Survival at 6-Months			Survival at 1-Year			Survival at 2-Years		
Exponential		87.0%	75.4%		79.4%	71.7%		63.3%	63.4%
Generalised Gamma		76.8%	75.6%		70.7%	72.5%		62.5%	63.8%
Gompertz	■	79.3%	75.6%	■	71.6%	73.0%	■	61.6%	64.8%
Log-Logistic		79.6%	75.7%		73.0%	72.4%		62.2%	63.7%
Log-Normal		79.0%	75.7%		72.5%	71.8%		62.2%	63.2%
Weibull		80.6%	75.6%		74.2%	72.5%		63.0%	63.7%

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Table 25. Observed and predicted estimates of overall survival

Distribution	Observed	Parametric	Semi-parametric	Observed	Parametric	Semi-parametric	Observed	Parametric	Semi-parametric
	Survival at 6-Months			Survival at 1-Year			Survival at 2-Years		
Exponential		93.7%	89.3%		89.7%	86.3%		80.6%	79.3%
Generalised Gamma		89.9%	88.4%		85.8%	84.3%		78.8%	78.0%
Gompertz	▪	89.7%	88.9%	▪	85.1%	84.3%	▪	78.1%	77.3%
Log-Logistic		90.6%	88.4%		86.7%	84.3%		79.2%	78.0%
Log-Normal		90.1%	88.4%		86.1%	83.8%		78.9%	77.7%
Weibull		90.8%	88.4%		87.0%	84.8%		79.6%	78.1%

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Figure 28. Comparison of OS, PFS and time on treatment extrapolations from CheckMate 142
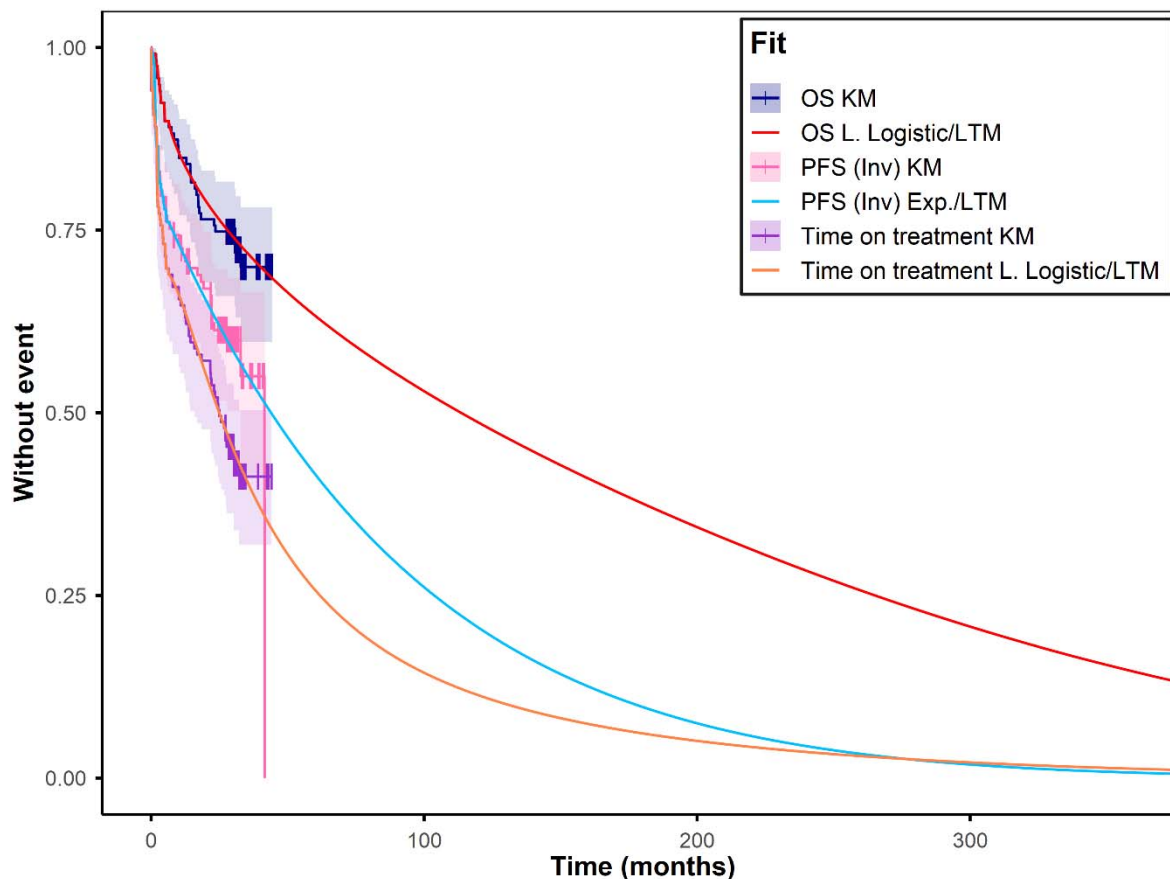
B.3.3.2.2 Comparators

In order to provide an unbiased assessment of the efficacy of standard of care, the base case analysis applies comparator efficacy derived from performing a MAIC analysis on studies identified from the SLR (Section B.2.9.1 and Appendix D).

By design, the MAIC described in Section B.2.9.2 provides a mean survival estimate as the primary output. As mean survival is the same as the area under the survival curve, changing the parametric fit does not impact the mean survival outcomes: the extrapolations must vary to fit the same mean survival output provided by the MAIC. Hence, in order to apply this MAIC-derived mean survival in the economic model, there are two potential methods for modelling the MAIC output: make a simple assumption of constant hazard (exponential fit) or make a more complex assumption around the hazard profile. As there is no available evidence to inform the hazard profile, it is assumed that the hazards remain constant, in line with Bagust and Beale (2014) rationale that this should be the default parametric function unless otherwise indicated.[113]

It is acknowledged that the assumption of constant hazards will have a minor impact on cost-effectiveness model outcomes, as the proportion of patients alive at each time may differ from

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the true survival distribution, though the area under the curve and thus overall time alive, pre and post progression is enforced to be that of the outcome of the MAIC. This has an impact firstly upon analyses at less than lifetime horizon, where the full area under the curve is not evaluated, and secondly as a result of the discounting rate. This latter impact is due to the fact that the exponential demonstrates less skew than the majority of survival distributions, thus more of the area under the curve is closer to model start and the reference time for discounting, so both costs and utilities are accrued at a lower discount rate than in a distribution with a longer "tail". This impact is minor, and extensive scenario analyses have been undertaken by looking at different clinical effectiveness data sources, which will have a greater impact of the hazard profile on comparator efficacy where mean survival remains the same.

Inputs describing the exponential survival function for comparators are provided in Table 26.

Table 26. Parameters describing exponential extrapolation of profession-free and overall survival for comparators

Comparator	MAIC evidence source	Mean PFS (months)	Mean OS (months)
BSC	RECOURSE/EUR[61]	2.1	7.6
FOLFIRI	VELOUR[93]	6.3	15.3
FOLFOX	CONFIRM2[94]	4.5	15.6
Irinotecan	PICCOLO[96]	6.7	15.4
Raltitrexed	Ugidos et al[97]	8.6	20.4
Trifluridine-tipiracil	RECOURSE/EUR[61]	4.2	10.9
BSC: best supportive care; OS: overall survival; PFS: progression-free survival. Exponential survival equation takes the form: S(t) = exp(-lambda*t)			

B.3.3.2.3 *All-cause mortality*

Individuals randomised into clinical trials are likely to be slightly younger and healthier than the overall CRC patient population in the UK. A total of 81/119 (68%) patients in the NIVO+IPI arm of the CheckMate 142 were under the age of 65 years, with a median age of 58.0 years,[83] increasing the likelihood that most deaths observed over the trial period were cancer-related.

Therefore, the model includes age and gender-adjusted mortality based on information from UK life tables,[116] described in Table 27. These values are included in every cycle in addition to the disease-related mortality values and are applied multiplicatively. While some form of double counting occurs, this effect applies equally to all comparators and is likely to have a minimal impact on predicted survival (and hence cost-effectiveness).

Table 27. Excerpt from England and Wales life tables[116]

Age	Probability of mortality*	
	Males	**Females**
50	0.003379	0.002169
51	0.003606	0.002358

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52	0.003907	0.002557
53	0.004125	0.002697
54	0.004478	0.002914
55	0.004760	0.003194
-	-	-
95	0.261012	0.228210
96	0.286714	0.250765
97	0.304113	0.267058
98	0.325892	0.291260
99	0.369540	0.309526
100	0.384386	0.343363
*Defined as the probability that a person aged *x* exact will die before reaching the age (*x*+1)		

B.3.3.3. Therapy effects

B.3.3.3.1 Treatment discontinuation

The economic model incorporates a time on treatment curve (described in Section B.3.3.3.1.2) to inform the proportion of patients discontinuing treatment due to progression and AEs. Additionally, the economic model includes discontinuation due to maximal treatment benefit (described in Section B.3.3.3.1.3). The timing of these discontinuations was assumed to impact on the incidence of AEs, treatment costs and resource use.

B.3.3.3.1.1.   Subsequent therapies

Following discontinuation, patients receive a subsequent therapy, outlined in Table 28. As a simplifying assumption, it is assumed that all patients receive BSC as subsequent therapy in the base case. As a scenario analysis, it is assumed that patients receiving NIVO+IPI, FOLFIRI or FOLFOX may receive trifluridine-tipiracil as a subsequent therapy, followed by BSC.

Table 28. Subsequent therapy applied in model

Treatment arm	Base case analysis (pre-progression and post-progression)	Scenario analysis (pre-progression and post-progression)
NIVO+IPI	BSC	Trifluridine-tipiracil , then BSC
BSC	BSC	-
FOLFIRI	BSC	Trifluridine-tipiracil , then BSC
FOLFOX	BSC	Trifluridine-tipiracil , then BSC
Irinotecan	BSC	-
Raltitrexed	BSC	-
Trifluridine-tipiracil	BSC	-

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B.3.3.3.1.2. Time on treatment

B.3.3.3.1.2.1. Nivolumab plus ipilimumab

A full description of extrapolation of discontinuation events is provided in Appendix M. In brief, patient-level data were obtained describing discontinuation due to progression, study drug toxicity, AEs unrelated to study therapy and withdrawal of patient consent.

Data informing this extrapolation were derived from the NIVO+IPI arm of CheckMate 142. In line with the survival analysis outlined in Section B.3.3.2.1, appropriateness of the extrapolation was evaluated by visual inspection of the fit, consideration of the log-cumulative hazard profile and minimisation of goodness-of-fit statistics (AIC and BIC). Based on this approach, a semi-parametric approach was considered to be most appropriate for modelling time on treatment, where Kaplan-Meier data was applied until 6.44 months followed by parametric extrapolation using the log-logistic distribution. Whilst the exponential distribution also provided an adequate fit, the log-logistic distribution provided less deviation from the Kaplan-Meier at 24 months for the base-case, which modelled discontinuation due to maximum clinical benefit, and also provided a long tail, representative of continued treatment post-progression.

Inputs are summarised Figure 29.

Figure 29. Time on treatment: CheckMate 142 NIVO+IPI – parametric extrapolations

B.3.3.3.1.2.2. Comparators

Comparator time on treatment has been derived from the published literature. Median estimates, outlined in Table 29, were applied in the economic model.

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Table 29. Comparator time on treatment

	Median time on treatment	Source
BSC*	6.76 weeks	RECOURSE[117]
FOLFIRI	8 cycles	VELOUR[93]
FOLFOX	4.3 months	CONFIRM 2[94]
Irinotecan	4 cycles	PICCOLO[118]
Raltitrexed	3 cycles	Ugidos 2019[97]
Trifluridine-tipiracil*	12.65 weeks	RECOURSE[117]
*mean time on treatment		

B.3.3.3.1.3. Discontinuation due to maximal clinical benefit

The SmPC for nivolumab and ipilimumab specifies that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[119] In terms of immunotherapies, this means that treatment may be discontinued in patients with limited clinical benefit.

Although no formal stopping rule was applied during CheckMate 142, clinicians and patients are aware that a stopping rule at two years is frequently applied for immunotherapies, and nivolumab specifically. In support of this, clinical experts consulted noted the use of a nivolumab stopping rule in other indications and considered it clinical practice in the treatment of mCRC, currently part of the Covid interim fund.[1] Further, evidence in support of a two-year stopping rule is currently being derived in the form of CheckMate 8HW, where a stopping rule was included in the protocol, and in CheckMate 142, where a protocol amendment in Feb 2019 included an optional stopping point. Hence, it is plausible that clinicians may informally apply this stopping rule in clinical practice, where patients have reached maximum clinical benefit.

During the undertaking of TA483[120] and TA484[121], the NICE Appraisal Committee noted that a 2-year stopping rule was not included in the pivotal trial or described in the SmPC and so queried whether clinicians would follow a stopping rule, especially if the patient was still benefiting from the treatment. When discussing the stopping rule, the committee noted comments on the second ACD that a two-year stopping rule is acceptable to both patients and clinicians and would be implementable.[120]

Given this evidence, it is considered appropriate to apply a stopping rule in the base case analysis. Patients still receiving treatment at two years are assumed to discontinue NIVO+IPI treatment and receive no further cost until progression. A scenario analysis is explored whereby no stopping rule is applied.

B.3.3.3.2 Adverse events

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

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AEs were selected on the basis of relevance to NIVO+IPI treatment. Grade 3-4 treatment-related AEs from CheckMate 142 were assessed if occurring in more than two patients, as outlined in Table 30. After exclusion of the most common AEs (transaminases increased; lipase increased) due to low cost profile, there were six AEs that occurred in at least three patients; all six were applied in the economic model. Of the remaining 11 AEs, four were identified for inclusion based on high cost per event.

Events are applied as a cost on initiation of treatment. It is assumed that AE disutilities are reflected by on treatment utility values.

Table 30. Rationale for adverse events in the economic model

| Adverse event	Proportion of patients experiencing in NIVO+IPI arm	Rationale for exclusion from economic model
██████████████	███	Low cost profile
████████████	███	Low cost profile
██████	███	Include
███████	███	Include
██████	███	Include
██████	███	Include
███████	███	Include
███	███	Include
███████████	███	Include
██████████████	███	Low incidence and lower cost
████████	███	Include
███████	███	Low incidence and lower cost
█████████	███	Low incidence and lower cost
████████████	███	Low incidence and lower cost
████████	███	Low incidence and lower cost
█████████	███	Low incidence and lower cost
█████████████	███	Include
██████	███	Include
██████	███	Low incidence and lower cost
Subset of AEs that were grade 3-4 treatment-related events occurring in at least 2 patients		

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Table 31. Grade 3-4 treatment-related adverse events applied in the economic model

	NIVO+IPI	BSC	FOLFIRI	FOLFOX	Irinotecan	Raltitrexed	Trifluridine-tipiracil
	CHECKMATE 142	RECOURSE[117]	VELOUR[93]*	CONFIRM 2[94]*	PICCOLO[118]*	Ugidos 2019[97]	RECOURSE[117]
N	119	265	605	420	218	NR	533
Colitis	■■■■	NR	NR	NR	NR	NR	NR
Diarrhoea	■■■■	0	7.80% (1.09%)	35 (8.33% [1.35%])	42 (19.27% [2.67%])	NR	12 (2.25% [0.64%])
Anaemia	■■■■	5 (1.89% [0.84%])	4.30% (0.82%)	NR	3 (1.38% [0.79%])	NR	65 (12.20% [1.42%])
Fatigue	■■■■	5 (1.89% [0.84%])	NR	31 (7.38% [1.28%])	24 (11.01% [2.12%])	NR	11 (2.06% [0.62%])
Hepatitis	■■■■	NR	NR	NR	NR	NR	NR
Rash	■■■■	NR	NR	NR	NR	NR	NR
Thrombocytopenia	■■■■	1 (0.38% [0.38%])	1.60% (0.51%)	17 (4.05% [0.96%])	0 (0%)	NR	9 (1.69% [0.56%])
Acute kidney injury	■■■■	NR	NR	NR	NR	NR	NR
Dyspnoea	■■■■	NR	NR	NR	NR	NR	NR
Hypophysitis	■■■■	NR	NR	NR	NR	NR	NR
NR: Not reported so assumed to be zero							
* AE causality not reported							

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B.3.4. *Measurement and valuation of health effects*

B.3.4.1. Health-related quality of life studies

In line with the NICE Guide to the methods of technology appraisal 2013[111], an SLR was conducted to identify health-related quality-of-life studies for the treatment of mCRC. In brief, electronic database searches (MEDLINE, Embase and grey literature) were conducted in January 2017, and subsequently updated in August 2020 (Figure 30). Full details of the process and methods to identify and select the relevant health-related quality-of-life evidence are summarised in Appendix H.

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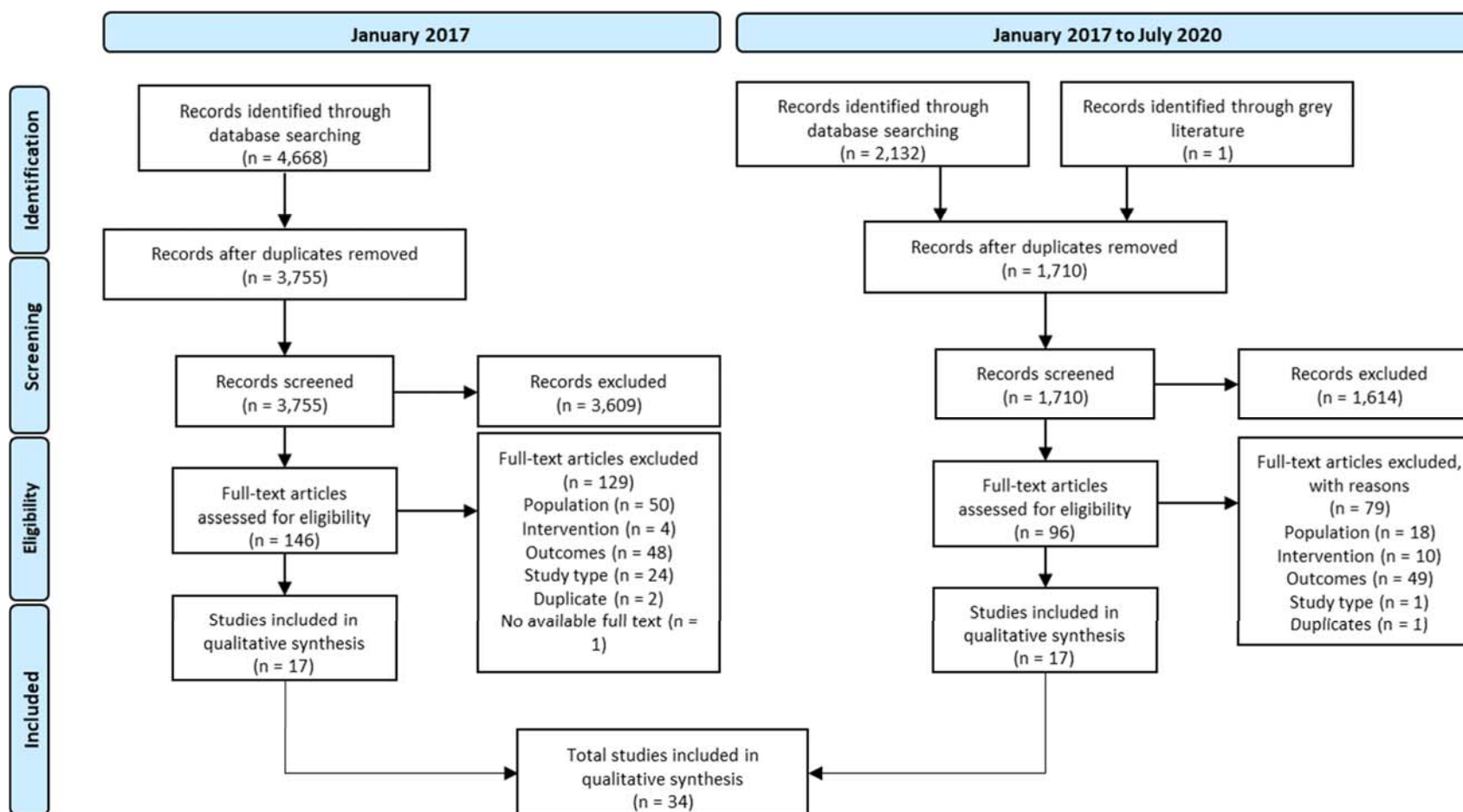
Figure 30. PRISMA diagram illustrating the study selection process for identifying health-related quality-of-life studies for the period from database inception to August 2020

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B.3.4.2. Health-related quality of life data from clinical trials

CheckMate 142 included assessment of health-related quality of life during the study, which can be used to derive utilities for scenario analysis. EQ-5D-3L was assessed prior to first dose of study treatment and every 6 weeks thereafter.[83] Following discontinuation of therapy, patients were assessed at two subsequent visits: 35±7 days after last dose; and 80±7 days after first visit.

In the NIVO+IPI arm, 119 patients were assessed, of which 117 patients had patient-reported outcome data and 107 patients had both baseline and post-baseline outcomes. Completed questionnaires were sourced from the February 2019 database lock for the overall population of CheckMate 142. Full patient-reported outcomes are reported in Section B.2.6.1.2, with a summary in Table 32.

Table 32. Summary of patient-reported outcome data from CheckMate 142 NIVO+IPI at baseline

	NIVO+IPI
EORTC QLQ-C30 global health status	63.7 (19.2)
EQ-5D-3L VAS	63.5 (24.0)
EQ-5D-3L Utility Index UK	0.714 (0.230)

As data were limited for patients who had discontinued treatment or experienced a progression event, an additional analysis was conducted assessing utility in patients receiving NIVO+IPI prior to discontinuation. Each EQ-5D-3L questionnaire was converted to utility using the UK EQ-5D-3L tariff and stratified by date of treatment discontinuation. If the questionnaire was prior to treatment discontinuation, it informed the on-treatment utility. Further details are available within Appendix N.

The mean on-treatment utility value was ▉▉ (SE: ▉▉). This can be considered higher than the utility values observed from the published literature (0.74 pre-progression;[122] 0.768 pre-progression[123]). Further, this is comparable with general population utility value (0.842). However, this is broadly equivalent to utility values observed from other nivolumab indications,[121, 124-128] indicating that this utility gain is due to the improvement in symptom burden available from NIVO+IPI.

This mean on-treatment utility value for NIVO+IPI includes measurements from patients who had clinically progressed but remained in receipt of the investigational therapy due to clinician discretion. As this discretion was provided if the clinician believed that there was clinical benefit to continuing treatment, these patients were thus expected to have a relatively high utility compared to other progressed patients, and it is consistent that though in a progressed state, they should receive the mean utility measured in their "on treatment" state.

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B.3.4.3. Mapping

EQ-5D-3L was collected alongside CheckMate 142; therefore, no mapping algorithms were used between patient-reported outcomes and EQ-5D to derive utilities.

B.3.4.4. Adverse reactions

It is assumed that AE disutilities are reflected by on treatment utility values. Hence, no further disutilities are applied.

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

The health utility of patients is dependent upon their disease state and so consequently, during each cycle, patients are assigned the health utility value equivalent to their current disease state. Age-dependent quality of life decrements are applied to patients relative to their age at model initiation, with decrements based on the estimated health utility of the general UK population; a smoothed fit to categorical quality of life decrement estimates, using the forecast function from Microsoft Excel, was utilised within the model.[129] The age-dependent decrement is calculated as in the following equation:

$UD = HU_b - HU_t$

where: UD = Utility decrement; HU_b = Health utility at baseline; and HU_t = Health utility at time t.

B.3.4.5.1 Rationale for application of treatment-specific CheckMate 142 values in economic evaluation

Pre- and post-progression utility in the comparator arm is derived from the CORRECT study,[122] as this is a recent study reporting evidence in a relevant mCRC population. Further, utility values are comparable with that applied in previous NICE HTAs, included TA242, TA307 and TA405. Hence, these utilities can be considered representative for comparator therapies.

Data from CheckMate 142 have been applied to describe utility for patients who are continuing to receive initial NIVO+IPI treatment in the economic evaluation. This approach should be considered consistent with the NICE reference case, as it reflects the trial evidence. However, due to a lack of adequate trial data to yield a post-progression utility, following discontinuation of NIVO+IPI, patients in the NIVO+IPI treatment arm receive values from the CORRECT study (i.e. equivalent to standard of care).

Improved utility can be expected in patients receiving NIVO+IPI. Immunotherapies have a different mechanism of action than conventional anti-cancer therapies and enable the patient's own immune system to directly destroy cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour through pre-existing, intrinsic processes.

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There are substantial clinical benefits for NIVO+IPI over comparators in previously treated MSI-H/dMMR mCRC that may be driving differences in utility. In particular, patients in the NIVO+IPI arm have improved PFS and OS. As utility in oncology is typically a function of time to death or time to progression, improved survival rates are a key component in postponing quality of life decrements.[130-134][115] Significantly, observed CheckMate 142 data demonstrate that there is a large pre-progression and post-progression survival benefit compared with comparators, supporting the impact of NIVO+IPI on quality of life. Further, the utility improvements for NIVO+IPI reflect the safety profile compared with chemotherapy.

The utility values observed during CheckMate 142 are broadly equivalent to utility values observed from other nivolumab and ipilimumab indications, [121, 124-126, 128, 135] indicating that this utility gain may be due to the novel mechanism of action. In addition, it is of note that pre- and post-progression utility estimates for comparator treatments were different from those estimated for nivolumab, consistent with the application of NIVO+IPI-specific utilities in this submission. As such, an assumption of treatment-specific utilities in the on-treatment phase only may be considered conservative.

Table 33: Summary of utility values observed for previous nivolumab or NIVO+IPI indications

Indication	Health state	Instrument	Utility estimate (mean)		Source study
			Nivolumab	Comparator^	
Renal cell carcinoma	Progression-free	EQ-5D	0.80	0.76	CheckMate 025[128]
	Progressed state		0.73	0.70	
	Progression-free*	EQ-5D-3L	0.793	0.751	CheckMate 214[136]
	Progressed state*		0.719	0.699	
SCCHN	Progression-free	EQ-5D-3L	0.74	0.69	CheckMate 141[121]
	Progressed state		0.66	0.56	
Melanoma	Pre-progression	EQ-5D-3L	0.7892	0.6963	CheckMate 066[125]
	Post-progression		0.7548	0.6565	
^Comparator treatments: RCC: everolimus; SCCHN: investigator's choice; melanoma: DTIC in CA209-066 and investigator's choice in CA209-037 * indicates trials investigating NIVO+IPI SCCHN: squamous cell carcinoma of the head and neck					

B.3.4.5.2 *Summary of health-related quality of life data applied in the economic model*

Table 34 summarised the health-related quality of life values applied in the economic model.

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Table 34. Summary of utility values for cost-effectiveness analysis

Comparator	State	Utility value mean (SE)	Source
NIVO+IPI	On treatment	■■■■■	CheckMate 142
	Off treatment	0.69 (0.07)	CORRECT[122]
Comparators	Pre-progression	0.75 (0.08)	CORRECT[122]
	Post-progression	0.69 (0.07)	
SE: standard error			

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

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1 Nivolumab plus ipilimumab costs

The costs of nivolumab, including drug procurement and administration, are applied each cycle, based on acquisition costs detailed in Table 35.

Table 35. Nivolumab dosing and acquisition cost

Dosing	3mg/kg by intravenous infusion over 30 mins every 3 weeks for 4 doses and then 240mg every 2 weeks thereafter
Dose per cycle	240 mg (221.1 mg assuming body weight 73.7 kg* and wastage of remainder of vial)
Cost (excluding PAS)	10mg/ml concentration for solution for infusion in vial, 4ml=£439.00; 10ml=£1,097.00; 24ml=£2,633.00
Cost per cycle	£2,633.00 (assuming wastage of remainder of vial).
Administration costs for nivolumab only	£241.06 (derived from costs detailed in Table 40), based on ERG comments from previous nivolumab appraisal.[121] Where patients receive nivolumab and ipilimumab on the same day, patients receive only the administration cost in Table 36
Total	£2,633.00 per treatment cycle (applied every 3 weeks for 4 cycles) £2,874.06 per treatment cycle (applied every 2 weeks from week 13)
Source: CheckMate 142 PLD [data on file]	

The costs of ipilimumab, including drug procurement and administration, are applied each cycle, based on acquisition costs detailed in Table 36.

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Table 36. Ipilimumab dosing and acquisition cost

Dosing	1mg/kg by intravenous infusion over 90 mins every 3 weeks for 4 doses
Dose per cycle	100 mg (73.7 mg assuming body weight 73.7 kg* and wastage of remainder of vial)
Cost (excluding PAS)	5mg/ml conc for soln for inf in vial, 10ml=£3,750.00; 40ml=£15,000.00
Cost per cycle	£7,500.00 (assuming wastage of remainder of vial)
Administration costs for nivolumab plus ipilimumab	£370.68 (derived from costs detailed in Table 40). Where patients receive nivolumab and ipilimumab on the same day, patients receive only this administration cost.
Total	£7,870.68 per treatment cycle (applied every 3 weeks for 4 cycles)
* Source: CheckMate 142 PLD [data on file]	

B.3.5.1.1.1. Proportion of patients receiving doses

The model utilises the application of a treatment cost adjustment based on the proportion of patients receiving a dose during CheckMate 142. The proportion is determined by a ratio of the actual doses received by the expected doses received, as presented in Table 37.

Table 37. Proportion of patients receiving doses in patients receiving nivolumab and ipilimumab

Treatment	Proportion of patients receiving doses
Nivolumab plus ipilimumab	93.5%
Nivolumab (from cycle 4)	96.1%

B.3.5.1.1.2. Patient Access Scheme

A Patient Access Scheme (PAS) has applied, comprising a discount of ■ from the nivolumab list price and ■ from the ipilimumab list price. In order to best replicate the true economic impact of a positive recommendation for nivolumab and ipilimumab, the economic evaluation presented in this submission applies the PAS in the base case analysis.

Table 38. Acquisition cost of nivolumab following application of PAS

	24 ml vial	Cost per cycle	
		Cycle 1-4	Cycle 5+
No PAS	£2,633.00	£2,633.00	£2,874.06
PAS	■	■	■
PAS: patient access scheme			

Table 39. Acquisition cost of ipilimumab following application of PAS

	10 ml vial	Cost per cycle
No PAS	£7,500.00	£7,870.68
PAS	■	■
PAS: patient access scheme		

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B.3.5.1.2 Administration costs

The costs of administration for NIVO+IPI and comparators are detailed in Table 40.

Table 40. Administration costs for nivolumab and comparators

Component	NHS cost collection data 2018-2019 code[137]	Cost (weighted average)
Deliver Simple Parenteral Chemotherapy at First Attendance	Weighted average of SB12Z codes (DCRDN: Daycase and Regular Day/Night; OP: Outpatient; Oth: Other)	£241.06
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	Weighted average of SB14Z codes (DCRDN: Daycase and Regular Day/Night; OP: Outpatient; Oth: Other)	£370.68
Deliver Exclusively Oral Chemotherapy	Weighted average of SB11Z codes (DCRDN: Daycase and Regular Day/Night; OP: Outpatient; Oth: Other)	£195.44

B.3.5.1.3 Comparators

Costs of comparator treatments are based on the costs required for each of the components:

- Chemotherapy costs
- Administration costs
- Subsequent therapy costs (composition detailed in section B.3.5.1.4)

For each component, the intervention cost, comprising acquisition cost, administration cost and BSC cost, was calculated on a per cycle basis. This was subsequently converted to a weekly cost over the course of each regimen (Table 41).

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Table 41. Comparator costs per cycle

Regimen	Components	Dosing instructions	Acquisition cost	Dose	Cost per dose	Admin cost	Cost per treatment cycle	Cycle length
BSC		Assumed equivalent between treatments arms	NA	NA	NA	NA	£0	NA
Trifluridine/ tipiracil[138]		35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs. Dosage for 1.79 m^2 body surface area is 60 mg twice daily[138]	15mg/6.14mg tablets, 20=£500.00; 60=£1,500.00 20mg/8.19mg tablets, 20=£666.67; 60=£2,000.00**[139]**	3 x 20mg/8.19mg tablets	£100.00	£195.44 per cycle	£2,195.44	28 days
Irinotecan monotherapy		350 mg/m^2 administered as an intravenous infusion over a 30- 90 minute period every three weeks[140]	20mg/ml concentrate for solution for infusion in vial, 2ml=£3.23; 5ml=£4.57; 15ml=£11.76; 25ml=£16.78[141]	1 x 2 ml vial, 1 x 5 ml vial, 1 x 25 ml vial	£24.58	£241.06 per cycle	£265.64	21 days
FOLFIRI	Fluorouracil (bolus)	400 mg/m^2 bolus on day 1	25mg/ml concentrate for solution for injection in vial, 10 x 20ml=£66.00; 100ml=£2.84 50mg/ml concentrate for solution for injection in vial, 10ml=£0.96; 20ml=£1.13; 50ml=£1.88; 100ml=£4.82[141]	1 x 1,000mg/20ml vial	£1.13	£370.68 per cycle	£392.77 for Cycle 1 £395.40 per remaining cycle	14 days
	Fluorouracil (IV)	2,400 mg/m^2 infusion over 46 hours	25mg/ml concentrate for solution for injection in vial, 10 x 20ml=£66.00; 100ml=£2.84	2 x 2,500mg/50ml vial	£3.76			

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Regimen	Components	Dosing instructions	Acquisition cost	Dose	Cost per dose	Admin cost	Cost per treatment cycle	Cycle length
			50mg/ml concentrate for solution for injection in vial, 10ml=£0.96; 20ml=£1.13; 50ml=£1.88; 100ml=£4.82[141]					
	Folinic acid	200 mg/m^2 infusion	10mg/ml solution for injection, al=£4.50; 10 x 5ml vial=£14.66; 10ml vial=£2.23; 10 x 10ml vial=£5.97; 30ml vial=£9.97; 35ml vial =£5.96; 10 x 35ml vial=£54.96. 7.5mg/ml solution for injection, 5 x 2ml amp=£35.32[141]	1 x 10 x 10ml vial	£5.97			
	Irinotecan	180 mg/m^2 intravenous infusion	20mg/ml concentrate for solution for infusion in vial, 2ml=£3.23; 5ml=£4.57; 15ml=£11.76; 25ml=£16.78[141]	1 x 2 ml vial, 1 x 15 ml vial	£14.99			
FOLFOX	Fluorouracil (bolus)	400 mg/m^2 bolus on day 1	25mg/ml concentrate for solution for injection in vial, 10 x 20ml=£66.00; 100ml=£2.84 50mg/ml concentrate for solution for injection in vial, 10ml=£0.96; 20ml=£1.13; 50ml=£1.88; 100ml=£4.82[141]	1 x 1,000mg/20ml vial	£1.13	£383.13 per cycle	£395.12 for Cycle 1 £397.75 per remaining cycle	14 days
	Fluorouracil (IV)	2,400 mg/m^2 infusion over 46 hours	25mg/ml concentrate for solution for injection in vial, 10 x 20ml=£66.00; 100ml=£2.84	2 x 2,500mg/50ml vial	£3.76			

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

Regimen	Components	Dosing instructions	Acquisition cost	Dose	Cost per dose	Admin cost	Cost per treatment cycle	Cycle length
			50mg/ml concentrate for solution for injection in vial, 10ml=£0.96; 20ml=£1.13; 50ml=£1.88; 100ml=£4.82[141]					
	Folinic acid	200 mg/m^2 infusion	10mg/ml solution for injection, al=£4.50; 10 x 5ml vial=£14.66; 10ml vial=£2.23; 10 x 10ml vial=£5.97; 30ml vial=£9.97; 35ml vial =£5.96; 10 x 35ml vial=£54.96. 7.5mg/ml solution for injection, 5 x 2ml amp=£35.32[141]	1 x 10 x 10ml vial	£5.97			
	Oxaliplatin	100 mg/m^2 infusion	5mg/ml solution for infusion in vial, 10ml=£7.19; 20ml=£8.67, 40ml= £18.78. [141]	2 x 40 ml vial	£17.34			
Raltitrexed		Max. 3mg/ m^2 IV infusion over 15 minutes	2mg powder for solution= £148.75[139]	3 x 2mg powder	£446.25	£241.06 per cycle	£687.31	21 days

BSC: best supportive care; FOLFIRI: 5-fluorouracil, folinic acid, irinotecan; FOLFOX: 5-fluorouracil, folinic acid, oxaliplatin; IV: intravenous therapy; NA: not appropriate; SLR: systematic literature review; SPC: Summary of Product Characteristics

Dosing based on 1.78 m^2 body surface area and 73.7 kg weight.

Trifluridine-tipiracil , irinotecan and capecitabine dosing based on SPC[138, 140, 142]; FOLFIRI and FOLFOX regimen component dosing based on most frequent reported in SLR; FOLFIRI and FOLFOX assumed to incur complex chemotherapy cost; irinotecan monotherapy infusion assumed to incur administration cost equivalent to nivolumab monotherapy cost.

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B.3.5.1.4 *Subsequent therapy*

The model incorporates treatment switching due to progression and discontinuation. Patients on NIVO+IPI and comparators are switched to subsequent treatment following discontinuation, while patients in the BSC arm remain on BSC until death. Subsequent therapies applied in the model are outlined in Table 42. The cost of subsequent therapy has been derived from that applied in TA405.[2]

As of the February 2019 database lock, ▇▇ of patients went on to receive non-study anti-tumour treatments following discontinuation of the study treatment.[87] Only ▇▇ of patients received subsequent systemic therapy. However, subsequent cancer therapy is plausible in UK clinical practice, although it should be noted that composition may not be comparable to CheckMate 142. In particular, EGFR inhibitors, VEGF inhibitors and regorafenib are not available in NHS England for previously treated mCRC patients. However, given the small patient numbers this is unlikely to impact on trial outcomes and is therefore does not form part of the base case.

Table 42. CheckMate 142: subsequent cancer therapy (February 2019 database lock)[87]

	Overall population (n = 119) n (%)
Patients who discontinue treatment	▇▇▇
Patients with subsequent therapy	▇▇▇
Radiotherapy	▇▇
Surgery	▇▇▇
Systemic therapy	▇▇▇
Oxaliplatin	▇▇
Irinotecan	▇▇
5-FU (fluorouracil, capecitabine)	▇▇
VEGF inhibitors	▇▇
EGFR inhibitors	▇▇
Regorafenib	▇▇
Trifluridine-tipiracil	▇▇
Investigational anti-cancer therapies	▇▇
Other	
Nivolumab	▇▇
FLUR/LEUCO/OXAL	▇▇
Lapatinib	▇▇
Trametinib	▇▇
Trastuzumab	▇▇
Calcium levofolinate	▇▇
Folinic acid	▇▇
Leucovorin	▇▇

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Patients may receive more than one therapy

To account for the costs of post-progression treatment, analysis was presented in the base case using RECOURSE trial data to provide an estimate of the average cost of post-progression treatment per patient.[2] No details were provided around the composition of this therapy, and only average total costs were available. The average cost of post-progression therapy is presented in Table 43. This cost is applied as a one-time cost for patients upon progression.

Table 43. Cost of subsequent therapy as reported in TA405

	Recourse (2014-2015 costs)[2]	Inflated to 2018-2019 costs
Average cost of post-progression therapy	£1,528.00	£1,621.21 (£324.24)
SE assumed to be 20% of mean value Inflation factor of 1.061[143]		

B.3.5.2. Health-state unit costs and resource use

Resource use estimates for the pre- and post-progression state were derived from those applied during the NICE appraisal of trifluridine-tipiracil,[2] summarised in Table 44, with the components of resource use listed in Table 45. Within the base case analysis, it was assumed that this resource use would apply throughout the treatment period for both NIVO+IPI and comparators. End of life costs are detailed in Table 46, and were applied as a one-time cost in the cycle prior to death.

Table 44. Monthly health state resource use and costs.

Component	Unit cost	Pre-progression*		Post-progression*	
		Use	Cost (SE)	Use	Cost (SE)
Medical oncologist outpatient consultation[ı]	£197.70	0	£197.70	0	£0.00
GP home consultation	£102.79	0	£0.00	0.25	£25.70
Community nurse specialist visit	£46.00	0	£0.00	1	£47.00
Health home visitor	£46.68	0.25	£11.67	1	£46.68
District nurse visit	£46.00	0	£0.00	1	£47.00
GP surgery visit	£39.00	0	£0.00	1	£39.00
Sum		£11.67 (£2.33)		£203.38 (£40.68)	
GP: general practitioner; SE: standard error.					
* In line with TA405[2], SE assumed to be 20% of mean value					
ı It is assumed that only BSC patients incur one Medical oncologist outpatient consultation, in line with TA405. All other patients would be seen by clinicians during their regularly scheduled administration visit.					

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Table 45. Resource unit cost sources

Resource	Unit cost source
Medical oncologist outpatient consultation	Weighted average of consultant led, medical oncology codes WF01A, WF01B, WF01C and WF01D from NHS Cost Collection 2018-19[137]
GP home consultation	GP out of surgery cost (£95.00) Table 10.8b, out of surgery visit lasting 23.4 minutes, PSSRU 2013[144] inflated from 2012/13 to 2018/19 using inflation factor 1.082.[143]
Community nurse specialist visit	Cost per working hour of band 6 nurse (£46.00), PSSRU 2019.[143]
Health home visitor	Cost per hour for health visitor (£44.00) from PSSRU 2015[145] inflated from 2014/15 to 2018/19 using inflation factor 1.061[146].
District nurse visit	Cost per working hour of band 6 nurse (£46.00), PSSRU 2019.[143]
GP surgery visit	Cost per surgery consultation £39.00) lasting 9.22 minutes, PSSRU 2019.

Table 46. End of life costs

	Round 2015 (2013-2014 costs)[147]			Inflated to 2018-2019 costs	
	Mean	Lower 95% CI	Upper 95% CI	Mean	SE
Health care	£4,854.00	£143.00	£14,485.00	£5,194.53	£3,841.70
Social care	£1,489.00	£44.00	£5,350.00	£1,593.46	£1,448.56
Total	£6,343.00			£6,787.99	£4,105.73

CI: confidence interval; SE: standard error.

Standard errors or reported costs from Round 2015[147] estimated from 95% confidence intervals. Standard error for the total estimated using the formula $SE_{total} = \sqrt{SE_{health}^2 + SE_{social}^2}$

Inflation factor of 1.061[143]

B.3.5.3. Adverse reaction unit costs and resource use

In order to provide an assessment of the costs associated with AEs, costs were sourced from recent NICE appraisals where possible, where costs were agreed with the ERG, and inflated to 2018-2019 costs.[143] These costs are summarised in Table 47.

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Table 47. Adverse event costs

Adverse event	Costs	SE	Source
Anaemia*	£855.05	£171.01	TA405[2]
Diarrhoea	£167.24	£33.45	National Cost Collection 2018/19. Total outpatient attendance, service code 300 for general medicine[137]
Dyspnoea*	£781.21	£156.24	Copley-Merriman et al. (2018). Average of inpatient and outpatient costs[148]
Fatigue	£167.24	£33.45	National Cost Collection 2018/19. Total outpatient attendance, service code 300 for general medicine[137]
Colitis*	£3,034.96	£606.99	Copley-Merriman et al. (2018). Inpatient and outpatient costs[148]
Hepatitis	£1,702.94	£340.59	National Cost Collection 2018/19. Total HRGs, currency codes GC17A – GC17K[137]
Acute kidney injury	£1,809.80	£361.96	National Cost Collection 2018/19. Total HRGs, currency codes LA07H – LA07P[137]
Rash	£167.24	£33.45	National Cost Collection 2018/19. Total outpatient attendance, service code 300 for general medicine[137]
Thrombocytopenia	£674.07	£134.81	National Cost Collection 2018/19. Total HRGs, currency codes SA12G – SA12K[137]
Hypopysitis*	£1,427.59	£285.52	Copley-Merriman et al. (2018). Average of inpatient and outpatient costs[148]
*costs inflated from 2014 costs using inflation factor of 1.070 All standard errors assumed to be 20% of mean value			

B.3.5.4. Miscellaneous unit costs and resource use

All costs and resource use has been detailed in Sections B.3.5.1 to B.3.5.3

Further information about how relevant cost and healthcare resource data were identified can be found in Appendix I.

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

B.3.6.1. Summary of base-case analysis inputs

Table 48. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Section
Baseline parameters			
Baseline parameters	Table 21	SE (age: normal; sex: beta)	B.3.2.2
Survival and progression functions			
Overall survival	Table 23	Described in Section B.3.3.2	B.3.3.2
Progression-free survival			
All-cause mortality	Table 27	None	B.3.3.2.3
Clinical parameters			
Discontinuations	Table 29	Described in Section B.3.3.2	B.3.3.3.1
AE prevalence	Table 31	SE (beta)	B.3.3.3.2
Utilities			
Health state utilities	Table 34	SE (beta)	B.3.4.5
Costs			
Medication costs	Table 35,Table 36,Table 41	Not applicable	B.3.5.1
Health state costs	Table 45	SE (gamma)	B.3.5.2
AE costs	Table 47	SE (gamma)	B.3.5.3
Subsequent therapy costs	Table 43	SE (gamma)	B.3.5.1.4
AE: adverse events; SE: standard error.			

B.3.6.2. Assumptions

A summary of the main assumptions within the economic model is provided within Table 49.

Table 49. Assumptions applied within the economic model

Assumption	Rationale	Section
Baseline parameters are derived from CheckMate 142 cohort, which is assumed to be reflective of patients seen in UK clinical practice for the anticipated MA.	Although there may be differences between characteristics in CheckMate 142 and mCRC patients in UK clinical practice, CheckMate 142 may be more representative of the types of patients who will be considered for treatment in clinical practice. Sensitivity analyses (probabilistic and deterministic) have been conducted to assess the impact of variability in these parameters, while scenarios assessed the impact of the differing clinical pathway on outcomes.	B.3.2.2
To reflect the nature of mCRC and available evidence, the model assumes that mCRC phases are consecutive, so that patients cannot revert to pre-	This assumption has been validated by clinicians and is line with other HTAs and economic analyses assessing the mCRC population.	B.3.2.3

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Assumption	Rationale	Section
progression from more advanced phases of the disease		
Weekly cycle length	Previous mCRC evaluations assessed by NICE have applied monthly[104], biweekly[104] and daily[2] cycle lengths; none of these cycle lengths have been considered inappropriate. This cycle length is short enough to reflect the treatment cycles for patients and reflects the frequency of follow-up for patients and a realistic minimum time during which the symptoms or response can change.	B.3.2.3
Comparator data is derived from the overall mCRC population and is assumed to reflect efficacy in the dMMR/MSI-H mCRC population	As described in Section B.1.3.2.1, outcomes may be poorer for dMMR/MSI-H mCRC patients receiving standard of care. It is therefore assumed that outcomes are equivalent between these two patient groups, with this likely to be conservative and bias against NIVO+IPI in economic evaluations.	B.3.3.1
Efficacy has been based on investigator-assessed data, rather than IRRC data	Progression within the model is applied based on investigator-assessed PFS from clinical studies, as this was used to define the primary endpoint (investigator-assessed ORR) in CheckMate 142. Further, investigator-assessed endpoints are likely to reflect clinician behaviour in a real-world setting. This may better reflect the accrual of costs and QALYs of CRC patients, as a patient considered not to have progressed by the clinician is likely to have a different quality of life and management plan compared with a patient considered to have progressed. A scenario analysis have been conducted to assess the impact of deriving efficacy inputs from BICR-assessed data, as presented in Section B.3.8.3.5.	B.3.2.3.1
Identification of most appropriate survival curves describing PFS, OS and discontinuation to inform extrapolation	Extensive analyses have been undertaken to identify appropriate and conservative survival curves describing NIVO+IPI efficacy, with reference to the guidance from the NICE Decision Support Unit (DSU)[112] and Bagust and Beale (2014)[113]. The approach and identified survival extrapolations have been validated by clinical and health economic experts. However, to address the uncertainty around this parameter, scenario analyses have been conducted by applying alternative assumptions around extrapolations, as presented in Section B.3.8.3.2.	B.3.3.2
Treatment is assumed to continue until either progression, discontinuation due to AEs (derived from NIVO+IPI patient-level data) or upon	This is likely to reflect clinical practice in most patients and with most therapies, and also provides a conservative assessment of incidence of discontinuation due to AEs during standard of care. Although no formal stopping rule was applied during CheckMate 142, clinicians and patients are aware that a stopping rule at two years is frequently applied for immunotherapies, and nivolumab specifically. Further, evidence in support of a two-year stopping rule is currently being derived in the form of CheckMate 8HW, where a stopping rule	B.3.3.3.1

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Assumption	Rationale	Section
reaching the two-year stopping rule.	was included in the protocol, and in CheckMate 142, where a protocol amendment in Feb 2019 included an optional stopping point. Hence, it is plausible that clinicians may informally apply this stopping rule in clinical practice, where patients have reached maximum clinical benefit. Alternative assumptions are assessed in scenario analysis.	
Utility values from CheckMate 142 reflect the on-treatment utility in the NIVO+IPI arm	As data were limited for patients who had discontinued treatment or experienced a progression event, utility values are split by on-treatment and off-treatment in the NIVO+IPI arm. This was deemed appropriate to reflect the improvement in quality-of-life associated with NIVO+IPI. An additional scenario analysis was conducted whereby utilities were applied by progression status and set equal to the comparator arms.	B.3.4.5
Source of adverse events for comparator treatments	Adverse events were sourced from CheckMate 142 for NIVO+IPI, whereas for the comparators of interest, estimates were derived from the systematic literature review. Immune-related adverse events were not modelled, due to the low incidence of grade 3-4 events and low cost of management. Further, evidence was not available to describe these events for comparators.	B.3.3.3.2
Medical resource use is derived from evidence presented during TA405	Robust estimates of medical resource use for patients in this setting are not publicly available, given the lack of alternative treatments available for which evidence may have previously been gathered. In order to provide relevant economic evaluations and facilitate comparison between these appraisals, medical resource use from TA405 is applied.	B.3.5.2
Post-progression treatment composition	In order to provide relevant economic evaluations and facilitate comparison between these appraisals, medical resource use from TA405 is applied to both treatment arms. As a simplifying assumption, it is assumed that all patients receive BSC as subsequent therapy in the base case, with the exception of BSC, where patients remain on BSC until death. As a scenario analysis, it is assumed that patients receiving NIVO+IPI, FOLFIRI or FOLFOX may receive trifluridine-tipiracil as a subsequent therapy, followed by BSC.	B.3.3.3.1.1

B.3.7. Base-case results

B.3.7.1. Base-case incremental cost-effectiveness analysis results

The results of the base-case analysis are summarised in Table 50.

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In terms of comparator treatments, the model predicts a median OS ranging from 0.441 (BSC) to 1.188 (raltitrexed) years, with a maximum accrual of 1.147 discounted QALYs over the modelled time horizon. By comparison, it was predicted that the use of NIVO+IPI will result up to an additional ▮▮▮ discounted QALYs (total: ▮▮▮ discounted QALYs) and an additional ▮▮▮ undiscounted life years (total: ▮▮▮ undiscounted life years), respectively. It was estimated that patients receiving NIVO+IPI would spend ▮▮▮ years in the pre-progression health, with a subsequent ▮▮▮ years in the post-progression health state, indicating that NIVO+IPI is associated with incremental benefit across all health states.

Total discounted costs associated with NIVO+IPI (with PAS), accrued over the modelled time horizon, were predicted to be ▮▮▮. By comparison, total discounted costs associated with comparators were notably lower. Incremental discounted costs were predicted to range between ▮▮▮ (versus trifluridine-tipiracil) to ▮▮▮ (versus BSC), under base case assumptions. The resulting ICER estimates for NIVO+IPI ranged from £13,367 per QALY (versus trifluridine-tipiracil) to £15,346 per QALY gain (versus raltitrexed). Therefore, the base case ICERs are all below a £50,000 per QALY willingness-to-pay threshold and NIVO+IPI can be considered a cost-effective use of NHS resources.

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Table 50. Base case analysis results

	NIVO+IPI	Trifluridine-tipiracil	BSC	FOLFOX	FOLFIRI	Irinotecan	Raltitrexed
Patient-level survival (undiscounted)							
Median ToT (years)	NR*	0.172	0.441	0.364	0.364	0.249	0.192
Mean ToT (years)	■	0.252	0.639	0.527	0.510	0.341	0.259
Median PFS (years)	■	0.249	0.134	0.268	0.383	0.402	0.517
Mean PFS (years)	■	0.359	0.185	0.384	0.537	0.567	0.729
Median OS (years)	■	0.632	0.441	0.920	0.901	0.901	1.188
Mean OS (years)	■	0.915	0.639	1.314	1.284	1.295	1.710
Patient-level progression							
Time in pre-progression (years)	■	0.359	0.185	0.384	0.537	0.567	0.729
Time in post-progression (years)	■	0.556	0.455	0.930	0.747	0.727	0.981
Time on treatment							
Time in initial therapy (years)	■	0.252	0.639	0.527	0.510	0.341	0.259
Time in subsequent therapy (years)	■	0.663	0.000	0.787	0.774	0.953	1.451
Costs (with PAS)							
HS costs	■	£7,930	£9,357	£8,691	£8,291	£8,244	£8,718
Treatment costs	■	£8,925	£0	£3,432	£3,175	£2,832	£4,670
AE costs for initial therapy	■	£123	£22	£54	£61	£62	£0
Total costs	■	£16,978	£9,379	£12,176	£11,527	£11,139	£13,389
Health benefits							
HS QALYs	■	0.634	0.443	0.891	0.881	0.889	1.158
Age-dependent utility	■	-0.003	-0.002	-0.007	-0.006	-0.007	-0.011
Total QALYs	■	0.630	0.441	0.884	0.874	0.883	1.147
Total LYs (undiscounted)	■	0.915	0.639	1.314	1.284	1.295	1.710
Incremental total costs	-	■	■	■	■	■	■
Incremental QALYs	-	■	■	■	■	■	■
Incremental LYs (undiscounted)	-	■	■	■	■	■	■
Cost/QALY	-	**£13,367**	**£14,211**	**£14,839**	**£14,930**	**£15,022**	**£15,346**

AE: adverse event; BSC: best supportive care; CR: complete remission; HS: health state; ICER: incremental cost-effectiveness ratio; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; IPI: ipilimumab; LY: life year; NIVO: nivolumab; OS: overall survival; PFS: progression-free survival; PR: partial response; QALY: quality-adjusted life year; SD: stable disease; ToT: Time on Treatment.
* median time on treatment not reached after application of stopping rule

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B.3.8. *Sensitivity analyses*

In the specific context of ██ ██ there are low patient numbers and poor survival outcomes. Additionally, there is a distinct paucity of evidence describing clinical practice on which to base economic evaluation. In general, where no evidence has been identified, simple assumptions have been made based on independent sources, such as published literature, CRC guidelines or previous NICE appraisals in the field of CRC. These assumptions were then assessed for clinical plausibility; uncertainty has been characterised through the use of sensitivity analyses.

In order to assess the impact of parameters on the model outcomes, deterministic sensitivity analyses have been used to vary the data inputs by a set amount. Uncertainty around the input data has been assessed using probabilistic analyses, while alternative assumptions have been examined in scenario analyses.

B.3.8.1. Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), a non-parametric bootstrapping approach was taken, sampling values from distributions around the means of input parameters in the model. Sampling utilises information of the mean and standard error of parameters to derive an estimated value using an appropriate distribution (costs: gamma, age and survival parameters: normal, utilities, probabilities and proportions: beta). These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters.

The majority of parameters included in the PSA are sampled independently, with the exception of semi-parametric survival estimates, where parameters associated with individual survival function are sampled using a common random number.

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

1,000 simulation of the model was deemed enough for the model results to converge to a sufficient degree of accuracy.

B.3.8.1.1 *PSA results*

Scatterplots for the base case analyses, arising from 1,000 simulations of the model with all parameters sampled are presented in Figure 31 to **Figure 36, while cost-effectiveness acceptability curves (CEACs) are presented in *Figure 37 to **Figure 42. Based on these analyses, the probability that NIVO+IPI is cost-effective versus trifluridine-tipiracil, BSC,

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FOLFOX, FOLFOX, irinotecan and raltitrexed is ▆▆, ▆▆ , ▆▆ , ▆▆ , ▆▆ and ▆▆, respectively, at a WTP threshold of £50,000 (Table 51. Base case results (probabilistic)).

Table 51. Base case results (probabilistic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	▆▆	▆▆	▆▆	-	-	-	-
Trifluridine-tipiracil	£17,070	0.909	0.646	▆▆	▆▆	▆▆	**£13,180**
Comparison B							
NIVO+IPI	▆▆	▆▆	▆▆	-	-	-	-
BSC	£9,357	0.650	0.458	▆▆	▆▆	▆▆	**£14,037**
Comparison C							
NIVO+IPI	▆▆	▆▆	▆▆	-	-	-	-
FOLFOX	£13,062	1.277	0.899	▆▆	▆▆	▆▆	**£14,474**
Comparison D							
NIVO+IPI	▆▆	▆▆	▆▆	-	-	-	-
FOLFIRI	£11,306	1.245	0.886	▆▆	▆▆	▆▆	**£14,752**
Comparison E							
NIVO+IPI	▆▆	▆▆	▆▆	-	-	-	-
Irinotecan	£11,094	1.269	0.904	▆▆	▆▆	▆▆	**£14,835**
Comparison F							
NIVO+IPI	▆▆	▆▆	▆▆	-	-	-	-
Raltitrexed	£14,194	1.9753	1.371	▆▆	▆▆	▆▆	**£15,577**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PSA: probabilistic sensitivity analysis; QALYs, quality-adjusted life years							

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Figure 31. ICER scatterplot: NIVO+IPI versus trifluridine-tipiracil

Figure 32. ICER scatterplot: NIVO+IPI versus BSC

Figure 33. ICER scatterplot: NIVO+IPI versus FOLFOX

Figure 34. ICER scatterplot: NIVO+IPI versus FOLFIRI

Figure 35. ICER scatterplot: NIVO+IPI versus irinotecan

Figure 36. ICER scatterplot: NIVO+IPI versus raltitrexed

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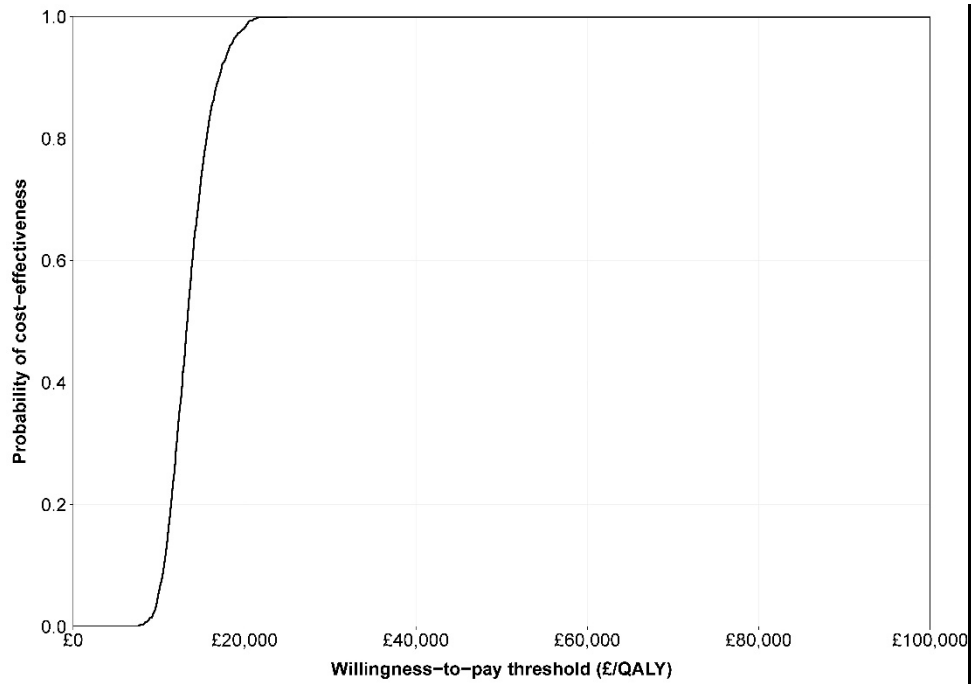
Figure 37. CEAC: NIVO+IPI versus trifluridine-tipiracil
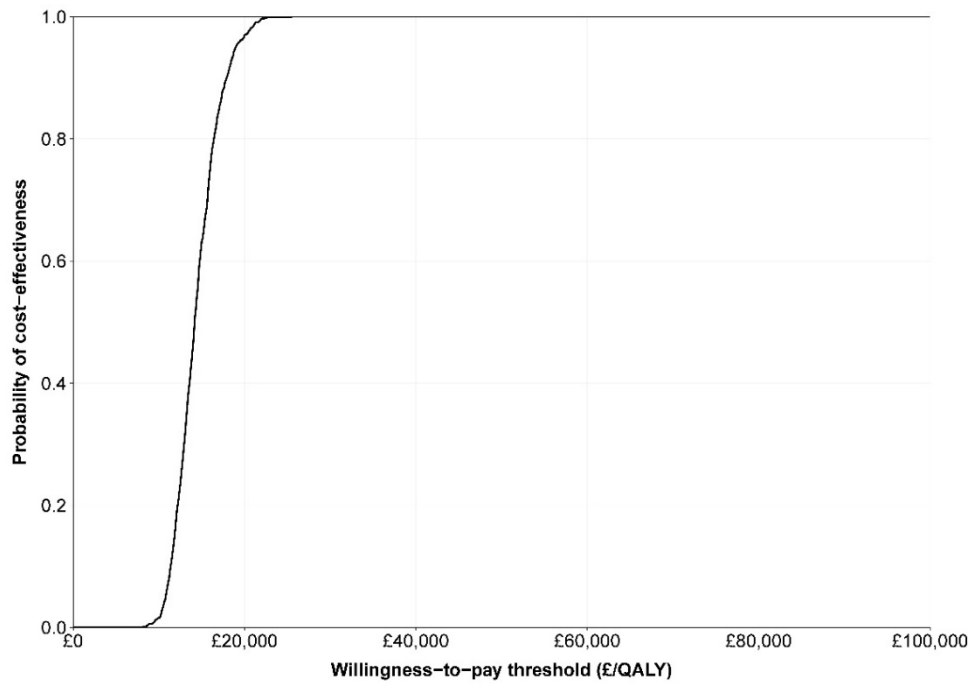
Figure 38. CEAC: NIVO+IPI versus BSC

Figure 39. CEAC: NIVO+IPI versus FOLFOX

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Figure 40. CEAC: NIVO+IPI versus FOLFIRI

Figure 41. CEAC: NIVO+IPI versus irinotecan

Figure 42. CEAC: NIVO+IPI versus raltitrexed

B.3.8.2. Deterministic sensitivity analysis

A range of one-way (deterministic) sensitivity analyses have been conducted, regarding the following assumption and parameters:

- Time horizon (5 and 10 years)
- Discounting: costs (0% and 6%)
- Discounting: benefits (0% and 6%)
- Baseline characteristics: age (± 20%, impacting on all-cause mortality)
- Baseline characteristics: sex (0% and 100% male, impacting on all-cause mortality)
- Health state costs: pre-progression, NIVO+IPI and comparators individually (± 20%)
- Health state costs: post-progression, NIVO+IPI and comparators individually (± 20%)
- Health state costs: death, NIVO+IPI and comparators individually (± 20%)
- Treatment costs: second line, NIVO+IPI and comparators individually (± 20%)
- Treatment costs: subsequent BSC, NIVO+IPI and comparators individually (± 20%)
- Adverse event costs (± 20%)
- Health state utility: pre-progression (for comparators), on treatment (for NIVO+IPI) (± 20%)
- Health state utility: post-progression (for comparators), off treatment (for NIVO+IPI) (± 20%)
- Proportion receiving dose, NIVO+IPI (± 20%)
- Second line adverse event prevalence, NIVO+IPI and comparators individually (± 20%)

Note: where (± 20%) is specified, the mean value is multiplied by 0.8 or 1.2 so to assess the impact of a 20% change in a value.

B.3.8.2.1 *Deterministic sensitivity analysis results*

Results of the deterministic sensitivity analysis is presented in Figure 43 to Figure 48 and demonstrates the impact of specific parameters on ICER estimates. In all scenarios, the ICER

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for NIVO+IPI versus comparators remained below the £50,000 per QALY willingness-to-pay threshold.

Plausible alternative scenarios have been investigated further in Section B.3.8.3.2, in order to assess the impact of the uncertainty in the analysis.
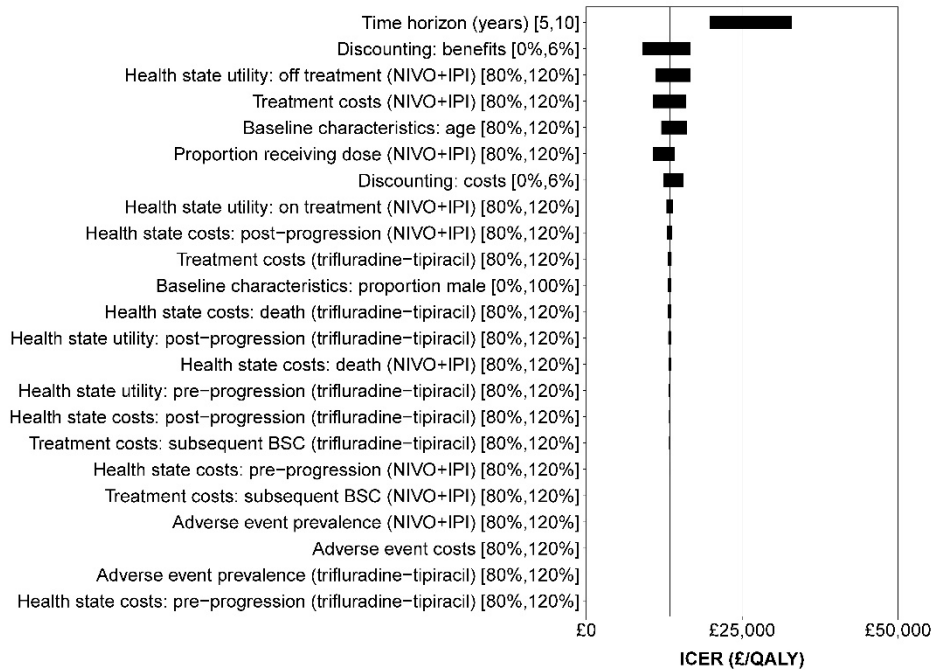
Figure 43. DSA tornado: NIVO+IPI versus trifluridine-tipiracil

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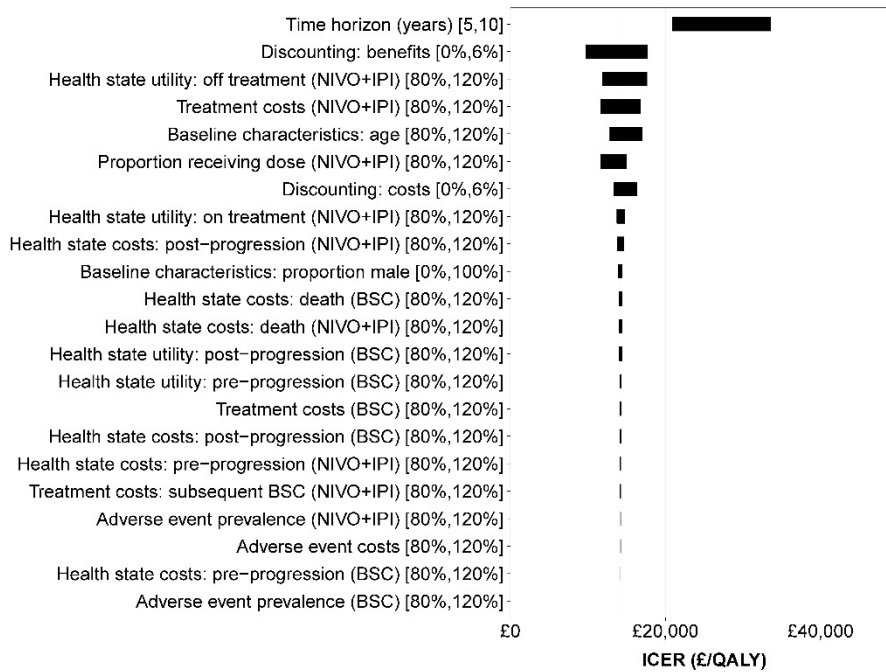
Figure 44. DSA tornado: NIVO+IPI versus BSC
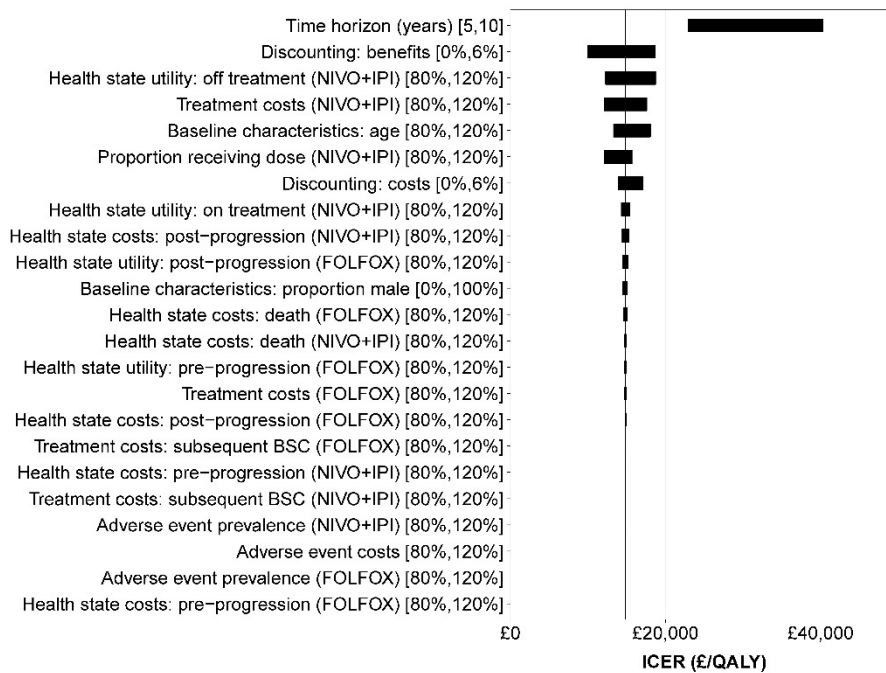
Figure 45. DSA tornado: NIVO+IPI versus FOLFOX

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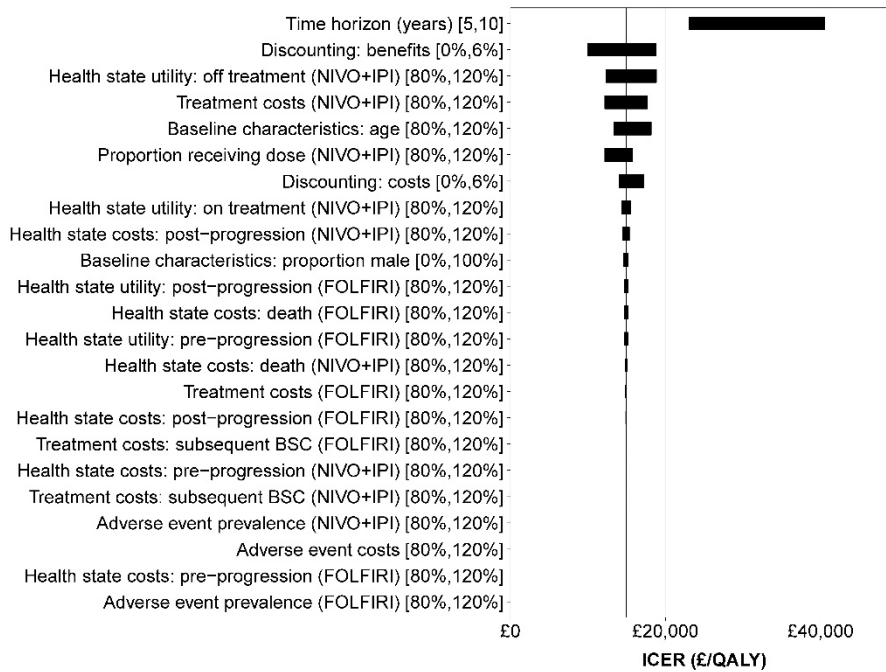
Figure 46. DSA tornado: NIVO+IPI versus FOLFIRI
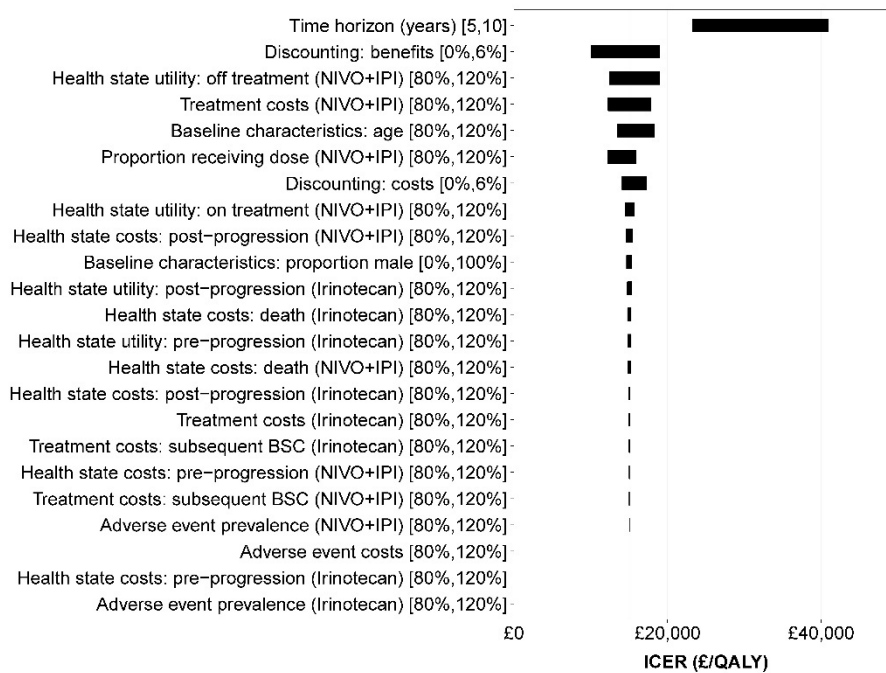
Figure 47. DSA tornado: NIVO+IPI versus irinotecan

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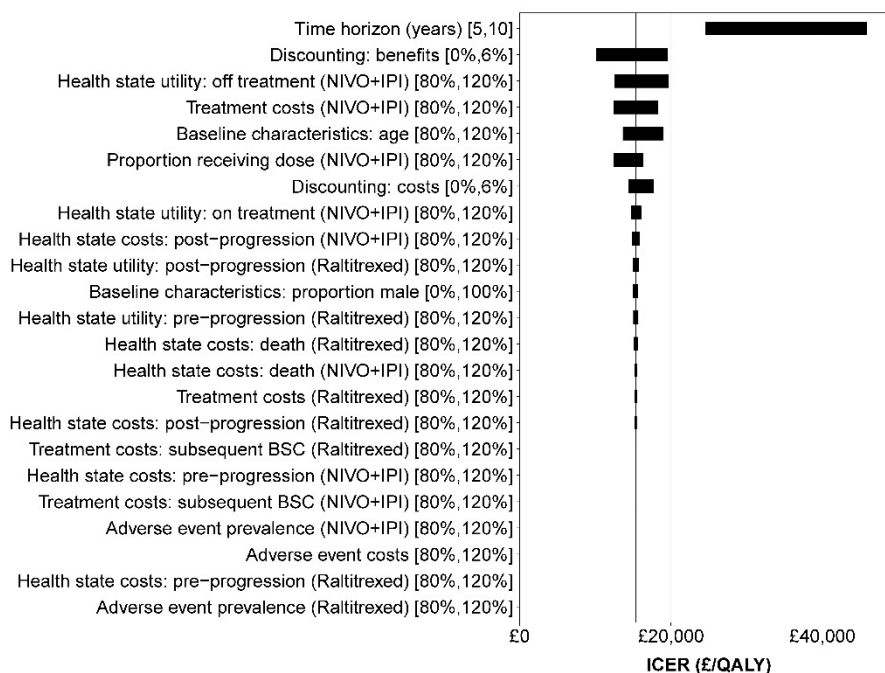
Figure 48. DSA tornado: NIVO+IPI versus raltitrexed

B.3.8.3. Scenario analysis

B.3.8.3.1   Threshold analysis

It is acknowledged that long-term extrapolation of NIVO+IPI survival adds uncertainty to the analysis. In order to assess the impact of the uncertainty on the analysis, the mean OS for NIVO+IPI were adjusted monotonically, deriving an exponential rate for use within the economic model.

Table 52 shows the mean OS and QALY gains required to be cost-effective at a £50,000 per QALY WTP threshold, with mean OS ranging from 34.2 months (versus BSC) to 49.1 months (versus raltitrexed) and incremental QALY gains ranging from 1.349 (versus trifluridine-tipiracil) to 1.498 (versus BSC).

Given that median OS has not been reached, despite ███████████████████████, it is extremely likely that the mean OS for NIVO+IPI reaches the threshold to be cost-effective at a £50,000/QALY threshold.

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Table 52. Threshold analysis: NIVO+IPI mean OS and incremental QALYs

Technologies	Nivo+Ipi mean OS required to be CE at £50,000/QALY (months)	Incremental QALYs required to be CE at £50,000/QALY
Trifluridine-tipiracil	35.1	1.349
BSC	34.2	1.498
FOLFOX	43.2	1.443
FOLFIRI	43.3	1.457
Irinotecan	43.7	1.465
Raltitrexed	49.1	1.421
BSC: best supportive care; CE: cost-effective; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; OS: overall survival; QALY: quality-adjusted life year		

B.3.8.3.2 *Alternative extrapolation of NIVO+IPI survival*

Survival modelling using long-term extrapolation of parametric functions is subject to considerable uncertainty despite efforts to robustly and transparently provide survival curves that best represent patients in clinical practice. In order to assess the impact of alternative parametric fittings on the cost-effectiveness of NIVO+IPI, survival curves described in the survival analysis report (Appendix M) have been applied within the model as scenario analyses.

This analysis should be viewed within the context of identifying the most appropriate survival extrapolation, as detailed in Section B.3.3.2. Parametric extrapolation of survival data from CheckMate 142 was undertaken with reference to the guidance from the NICE Decision Support Unit (DSU)[112] and Bagust and Beale (2014)[113]. All extrapolations have been assessed for completeness. However, it should be noted that several of these extrapolations are not considered appropriate. Clinically implausible fits are presented in grey italics and are defined as extrapolations that exceed the 95% confidence intervals of the Kaplan-Meier data or provides mean survival that cannot be considered plausible. The impact of applying alternative survival extrapolations for the NIVO+IPI arm (PFS, OS and time on treatment) in the base case analysis is shown in Table 53 to Table 58 and Figure 49 to Figure 66. For PFS, all the alternative parametric extrapolations in grey italics were considered implausible because these extrapolations exceeded the 95% confidence intervals of the Kaplan-Meier data. For OS, the parametric extrapolation using the exponential distribution was considered implausible because the extrapolation exceeded the 95% confidence intervals of the Kaplan-Meier data, whereas the gompertz was deemed implausible due to the long mean survival time. For time on treatment, both the exponential and gompertz parametric extrapolations were considered implausible because the extrapolations exceeded the 95% confidence intervals of the Kaplan-Meier data, as well as providing a poor visual fit to the data.

Predicted discounted incremental QALYs ranged from ███ to ███, with variation in discounted incremental costs of ███ to ███. This had an associated impact on ICERs versus the comparators, which ranged between £11,410 per QALY (when a semi-parametric

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gompertz curve was applied for OS versus trifluridine-tipiracil) and £20,046 per QALY (when a semi-parametric exponential curve was applied for OS versus raltitrexed).

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Table 53. Scenario analysis: impact of alternative NIVO+IPI survival extrapolations versus trifluridine-tipiracil

Scenario			NIVO+IPI versus trifluridine-tipiracil		
			Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
PFS	Parametric	*Exponential*	■	■	*£13,825*
		Generalised Gamma	■	■	£12,112
		Gompertz	■	■	*£11,799*
		Log-logistic	■	■	*£12,734*
		Log-normal	■	■	*£12,646*
		Weibull	■	■	*£13,129*
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£13,367
		Generalised Gamma	■	■	£14,024
		Gompertz	■	■	£14,154
		Log-logistic	■	■	£13,120
		Log-normal	■	■	£12,682
		Weibull	■	■	£13,610
OS	Parametric	*Exponential*	■	■	*£17,994*
		Generalised Gamma	■	■	£13,016
		Gompertz	■	■	*£11,331*
		Log-logistic	■	■	£13,916
		Log-normal	■	■	£13,268
		Weibull	■	■	£14,840
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£16,803
		Generalised Gamma	■	■	£13,685
		Gompertz	■	■	£11,410
		Log-logistic	■	■	£13,367
		Log-normal	■	■	£12,579
		Weibull	■	■	£13,967
ToT	Parametric	*Exponential*	■	■	*£14,504*
		Generalised Gamma	■	■	£13,296
		Gompertz	■	■	*£13,360*
		Log-logistic	■	■	£13,098
		Log-normal	■	■	£12,877
		Weibull	■	■	£13,203
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£13,222
		Generalised Gamma	■	■	£13,348
		Gompertz	■	■	£13,317
		Log-logistic	■	■	£13,367
		Log-normal	■	■	£13,323
		Weibull	■	■	£13,379
ICER: incremental cost-effectiveness ratio; Inc: incremental; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time on treatment					
Grey italics denotes highly implausible extrapolations, defined as extrapolations that exceed the 95% confidence intervals of the Kaplan-Meier data or provides mean survival that cannot be considered plausible.					

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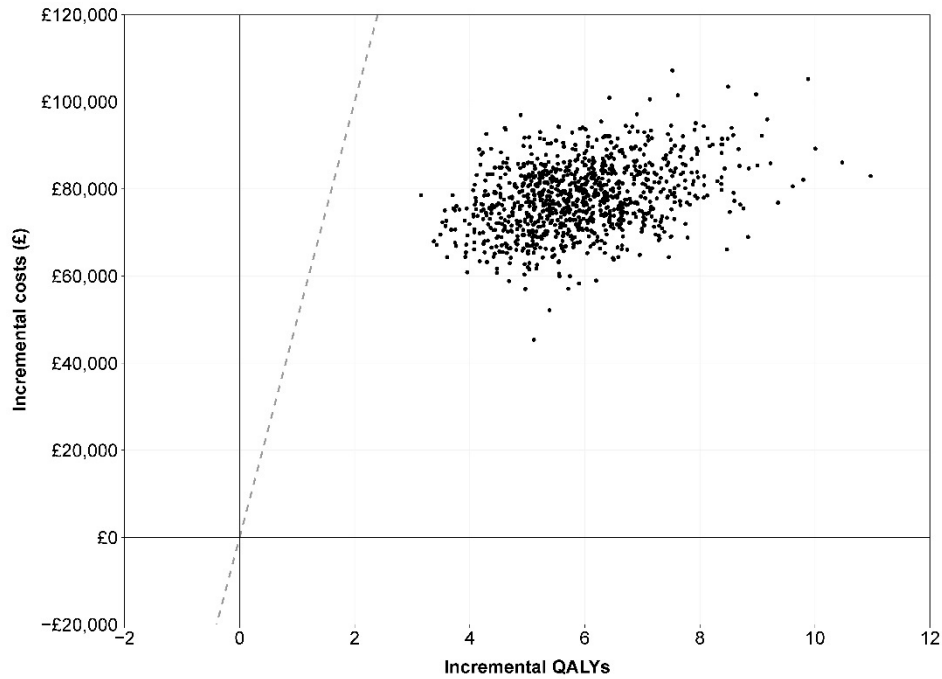
Table 54. Scenario analysis: impact of alternative NIVO+IPI survival extrapolations versus BSC

Scenario			NIVO+IPI versus BSC		
			Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
PFS	Parametric	*Exponential*	■	■	*£14,655*
		Generalised Gamma	■	■	£12,996
		Gompertz	■	■	*£12,692*
		Log-logistic	■	■	*£13,598*
		Log-normal	■	■	*£13,512*
		Weibull	■	■	*£13,980*
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£14,211
		Generalised Gamma	■	■	£14,847
		Gompertz	■	■	£14,973
		Log-logistic	■	■	£13,972
		Log-normal	■	■	£13,548
		Weibull	■	■	£14,446
OS	Parametric	*Exponential*	■	■	*£19,010*
		Generalised Gamma	■	■	£13,842
		Gompertz	■	■	*£12,053*
		Log-logistic	■	■	£14,788
		Log-normal	■	■	£14,107
		Weibull	■	■	£15,755
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£17,788
		Generalised Gamma	■	■	£14,546
		Gompertz	■	■	£12,138
		Log-logistic	■	■	£14,211
		Log-normal	■	■	£13,380
		Weibull	■	■	£14,842
ToT	Parametric	*Exponential*	■	■	*£15,310*
		Generalised Gamma	■	■	£14,142
		Gompertz	■	■	*£14,204*
		Log-logistic	■	■	£13,951
		Log-normal	■	■	£13,737
		Weibull	■	■	£14,053
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£14,071
		Generalised Gamma	■	■	£14,192
		Gompertz	■	■	£14,162
		Log-logistic	■	■	£14,211
		Log-normal	■	■	£14,168
		Weibull	■	■	£14,223
ICER: incremental cost-effectiveness ratio; Inc: incremental; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time on treatment					
Grey italics denotes highly implausible extrapolations, defined as extrapolations that exceed the 95% confidence intervals of the Kaplan-Meier data or provides mean survival that cannot be considered plausible.					

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Table 55. Scenario analysis: impact of alternative NIVO+IPI survival extrapolations versus FOLFOX

Scenario			NIVO+IPI versus FOLFOX		
			Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
PFS	Parametric	*Exponential*	███	███	*£15,318*
		Generalised Gamma	███	███	£13,527
		Gompertz	███	███	*£13,200*
		Log-logistic	███	███	*£14,178*
		Log-normal	███	███	*£14,085*
		Weibull	███	███	*£14,590*
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	███	███	£14,839
		Generalised Gamma	███	███	£15,526
		Gompertz	███	███	£15,662
		Log-logistic	███	███	£14,581
		Log-normal	███	███	£14,123
		Weibull	███	███	£15,093
OS	Parametric	*Exponential*	███	███	*£20,533*
		Generalised Gamma	███	███	£14,418
		Gompertz	███	███	*£12,410*
		Log-logistic	███	███	£15,502
		Log-normal	███	███	£14,721
		Weibull	███	███	£16,626
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	███	███	£19,044
		Generalised Gamma	███	███	£15,223
		Gompertz	███	███	£12,504
		Log-logistic	███	███	£14,839
		Log-normal	███	███	£13,894
		Weibull	███	███	£15,565
ToT	Parametric	*Exponential*	███	███	*£16,023*
		Generalised Gamma	███	███	£14,765
		Gompertz	███	███	*£14,831*
		Log-logistic	███	███	£14,558
		Log-normal	███	███	£14,328
		Weibull	███	███	£14,668
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	███	███	£14,688
		Generalised Gamma	███	███	£14,819
		Gompertz	███	███	£14,787
		Log-logistic	███	███	£14,839
		Log-normal	███	███	£14,793
		Weibull	███	███	£14,851
ICER: incremental cost-effectiveness ratio; Inc: incremental; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time on treatment					
Grey italics denotes highly implausible extrapolations, defined as extrapolations that exceed the 95% confidence intervals of the Kaplan-Meier data or provides mean survival that cannot be considered plausible.					

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Table 56. Scenario analysis: impact of alternative NIVO+IPI survival extrapolations versus FOLFIRI

Scenario			NIVO+IPI versus FOLFIRI		
			Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
PFS	Parametric	*Exponential*	■	■	*£15,409*
		Generalised Gamma	■	■	£13,621
		Gompertz	■	■	*£13,294*
		Log-logistic	■	■	*£14,270*
		Log-normal	■	■	*£14,177*
		Weibull	■	■	*£14,682*
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£14,930
		Generalised Gamma	■	■	£15,616
		Gompertz	■	■	£15,752
		Log-logistic	■	■	£14,673
		Log-normal	■	■	£14,215
		Weibull	■	■	£15,184
OS	Parametric	*Exponential*	■	■	*£20,656*
		Generalised Gamma	■	■	£14,506
		Gompertz	■	■	*£12,485*
		Log-logistic	■	■	£15,598
		Log-normal	■	■	£14,811
		Weibull	■	■	£16,728
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£19,159
		Generalised Gamma	■	■	£15,317
		Gompertz	■	■	£12,579
		Log-logistic	■	■	£14,930
		Log-normal	■	■	£13,979
		Weibull	■	■	£15,660
ToT	Parametric	*Exponential*	■	■	*£16,112*
		Generalised Gamma	■	■	£14,856
		Gompertz	■	■	*£14,923*
		Log-logistic	■	■	£14,650
		Log-normal	■	■	£14,421
		Weibull	■	■	£14,760
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£14,779
		Generalised Gamma	■	■	£14,910
		Gompertz	■	■	£14,878
		Log-logistic	■	■	£14,930
		Log-normal	■	■	£14,884
		Weibull	■	■	£14,943
ICER: incremental cost-effectiveness ratio; Inc: incremental; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time on treatment					
Grey italics denotes highly implausible extrapolations, defined as extrapolations that exceed the 95% confidence intervals of the Kaplan-Meier data or provides mean survival that cannot be considered plausible.					

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Table 57. Scenario analysis: impact of alternative NIVO+IPI survival extrapolations versus irinotecan

Scenario			NIVO+IPI versus irinotecan		
			Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
PFS	Parametric	*Exponential*	■	■	*£15,502*
		Generalised Gamma	■	■	£13,711
		Gompertz	■	■	*£13,383*
		Log-logistic	■	■	*£14,361*
		Log-normal	■	■	*£14,268*
		Weibull	■	■	*£14,774*
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£15,022
		Generalised Gamma	■	■	£15,709
		Gompertz	■	■	£15,845
		Log-logistic	■	■	£14,764
		Log-normal	■	■	£14,306
		Weibull	■	■	£15,276
OS	Parametric	*Exponential*	■	■	*£20,808*
		Generalised Gamma	■	■	£14,594
		Gompertz	■	■	*£12,554*
		Log-logistic	■	■	£15,696
		Log-normal	■	■	£14,902
		Weibull	■	■	£16,838
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£19,295
		Generalised Gamma	■	■	£15,413
		Gompertz	■	■	£12,649
		Log-logistic	■	■	£15,022
		Log-normal	■	■	£14,062
		Weibull	■	■	£15,760
ToT	Parametric	*Exponential*	■	■	*£16,205*
		Generalised Gamma	■	■	£14,948
		Gompertz	■	■	*£15,015*
		Log-logistic	■	■	£14,742
		Log-normal	■	■	£14,512
		Weibull	■	■	£14,852
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£14,871
		Generalised Gamma	■	■	£15,002
		Gompertz	■	■	£14,970
		Log-logistic	■	■	£15,022
		Log-normal	■	■	£14,976
		Weibull	■	■	£15,035

ICER: incremental cost-effectiveness ratio; Inc: incremental; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time on treatment

Grey italics denotes highly implausible extrapolations, defined as extrapolations that exceed the 95% confidence intervals of the Kaplan-Meier data or provides mean survival that cannot be considered plausible.

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Table 58. Scenario analysis: impact of alternative NIVO+IPI survival extrapolations versus raltitrexed

Scenario			NIVO+IPI versus raltitrexed		
			Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
PFS	Parametric	*Exponential*	■	■	*£15,849*
		Generalised Gamma	■	■	£13,969
		Gompertz	■	■	*£13,625*
		Log-logistic	■	■	*£14,652*
		Log-normal	■	■	*£14,554*
		Weibull	■	■	*£15,085*
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£15,346
		Generalised Gamma	■	■	£16,067
		Gompertz	■	■	£16,209
		Log-logistic	■	■	£15,075
		Log-normal	■	■	£14,594
		Weibull	■	■	£15,613
OS	Parametric	*Exponential*	■	■	*£21,754*
		Generalised Gamma	■	■	£14,884
		Gompertz	■	■	*£12,710*
		Log-logistic	■	■	£16,076
		Log-normal	■	■	£15,216
		Weibull	■	■	£17,322
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£20,046
		Generalised Gamma	■	■	£15,768
		Gompertz	■	■	£12,810
		Log-logistic	■	■	£15,346
		Log-normal	■	■	£14,313
		Weibull	■	■	£16,144
ToT	Parametric	*Exponential*	■	■	*£16,586*
		Generalised Gamma	■	■	£15,268
		Gompertz	■	■	*£15,338*
		Log-logistic	■	■	£15,051
		Log-normal	■	■	£14,811
		Weibull	■	■	£15,167
	Semi-parametric with Kaplan-Meier to 6.44 months	Exponential	■	■	£15,187
		Generalised Gamma	■	■	£15,324
		Gompertz	■	■	£15,291
		Log-logistic	■	■	£15,346
		Log-normal	■	■	£15,297
		Weibull	■	■	£15,359

ICER: incremental cost-effectiveness ratio; Inc: incremental; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time on treatment

Grey italics denotes highly implausible extrapolations, defined as extrapolations that exceed the 95% confidence intervals of the Kaplan-Meier data or provides mean survival that cannot be considered plausible.

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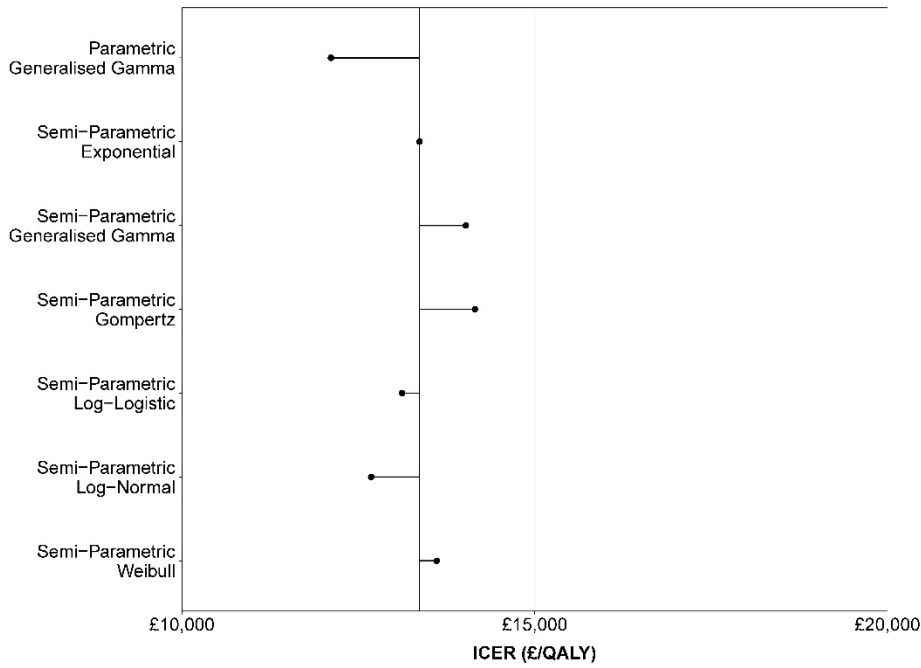
Figure 49. Scenario analysis: impact of alternative NIVO+IPI PFS extrapolations versus trifluridine-tipiracil
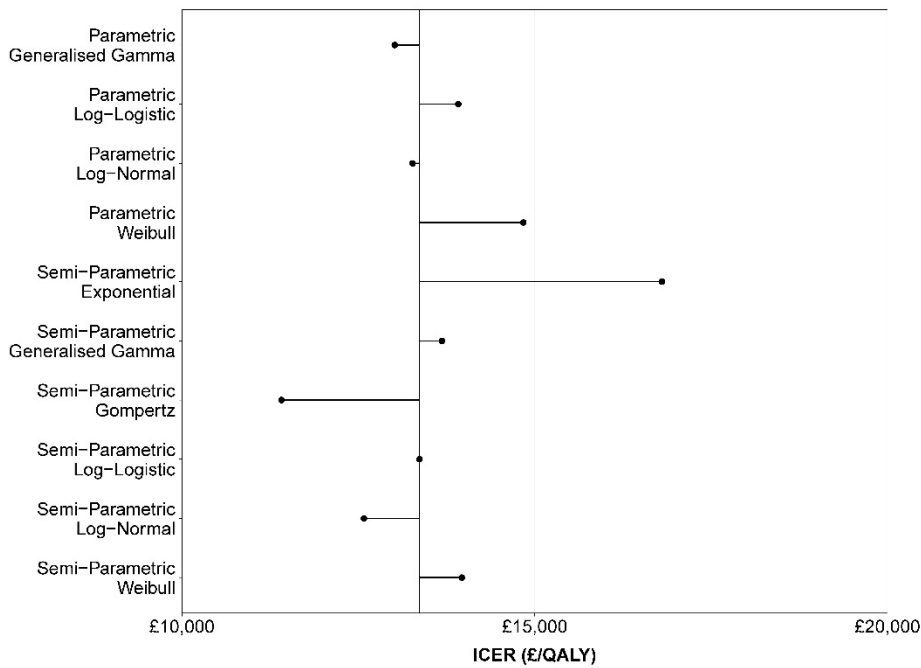
Figure 50. Scenario analysis: impact of alternative NIVO+IPI OS extrapolations versus trifluridine-tipiracil

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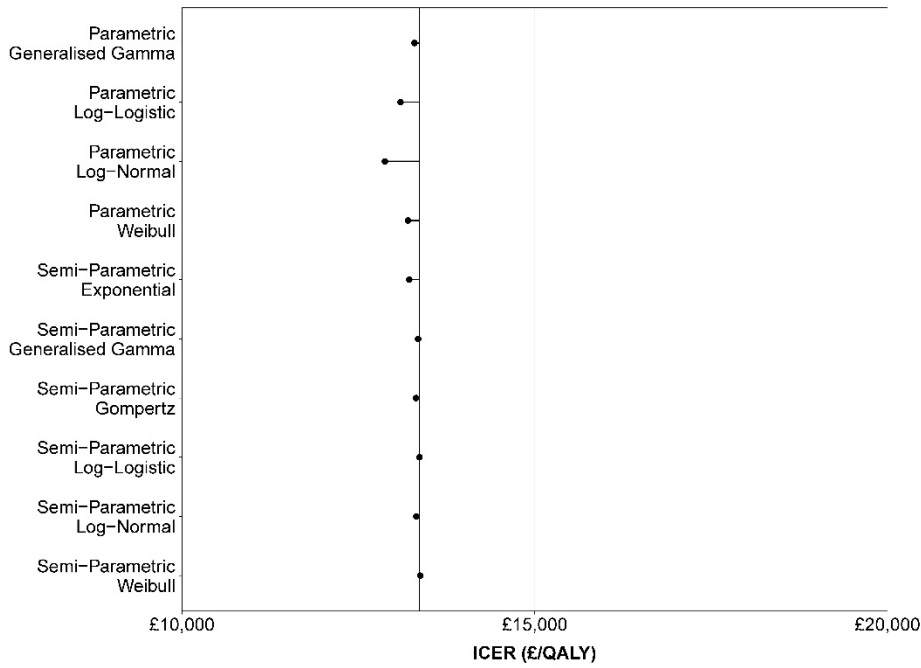
Figure 51. Scenario analysis: impact of alternative NIVO+IPI time on treatment extrapolations versus trifluridine-tipiracil
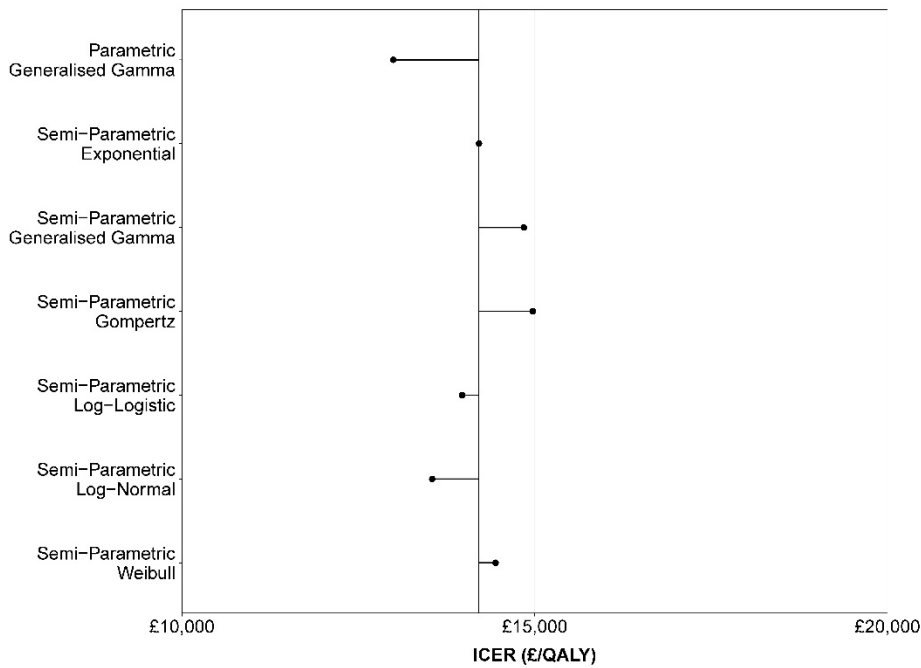
Figure 52. Scenario analysis: impact of alternative NIVO+IPI PFS extrapolations versus BSC

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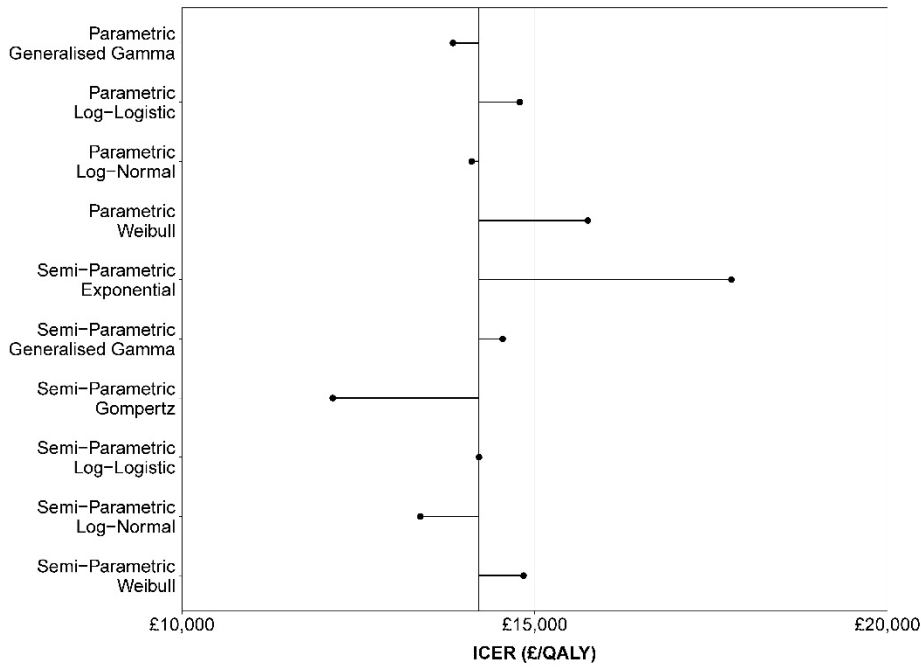
Figure 53. Scenario analysis: impact of alternative NIVO+IPI OS extrapolations versus BSC
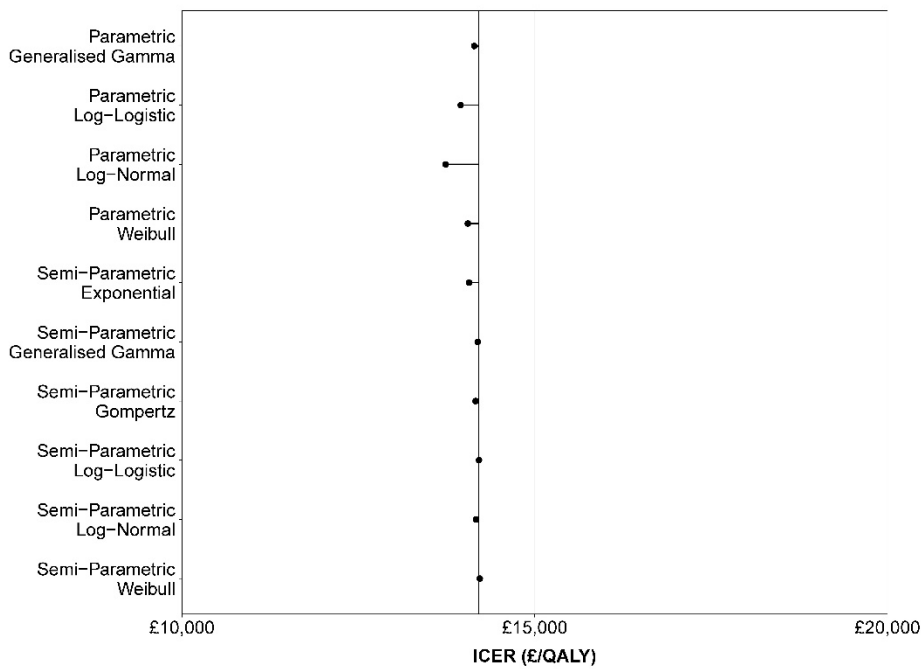
Figure 54. Scenario analysis: impact of alternative NIVO+IPI time on treatment extrapolations versus BSC

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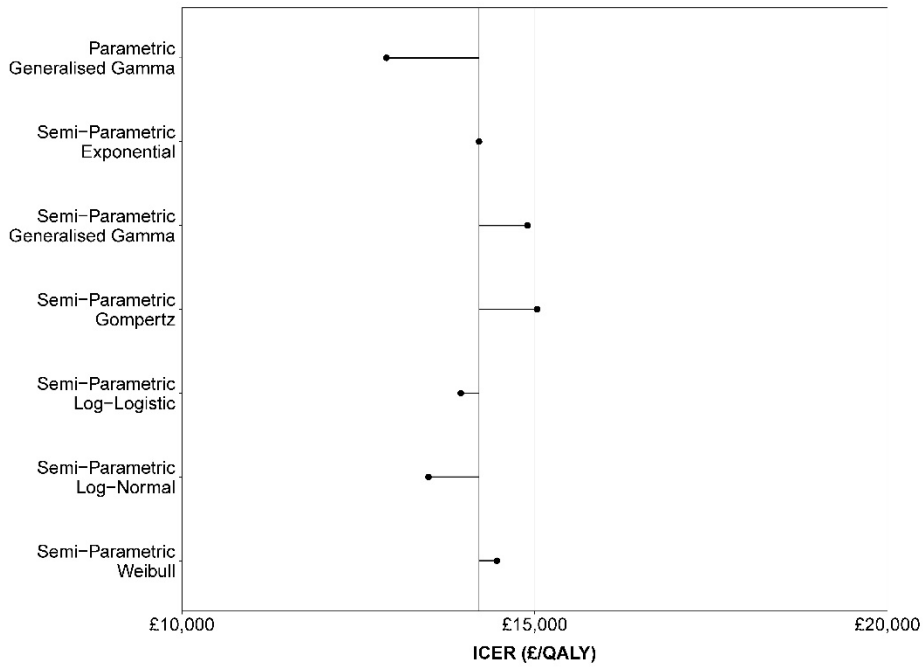
Figure 55. Scenario analysis: impact of alternative NIVO+IPI PFS extrapolations versus FOLFOX
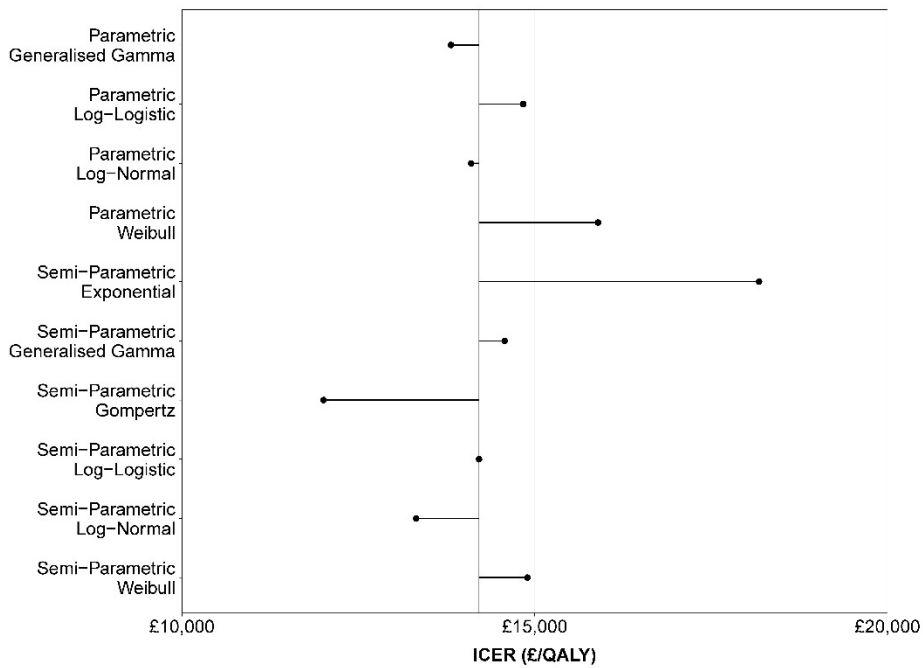
Figure 56. Scenario analysis: impact of alternative NIVO+IPI OS extrapolations versus FOLFOX

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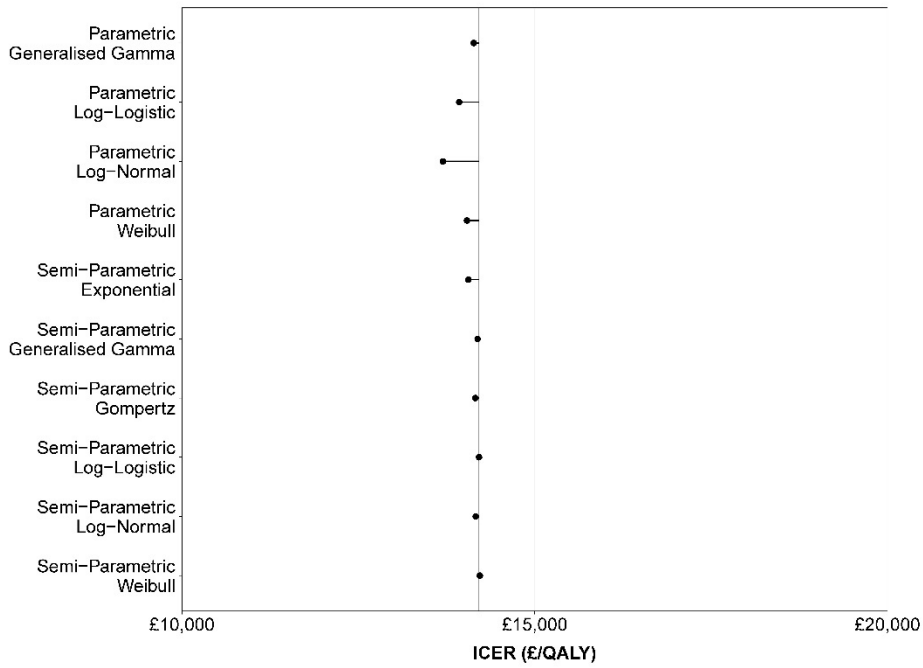
Figure 57. Scenario analysis: impact of alternative NIVO+IPI time on treatment extrapolations versus FOLFOX
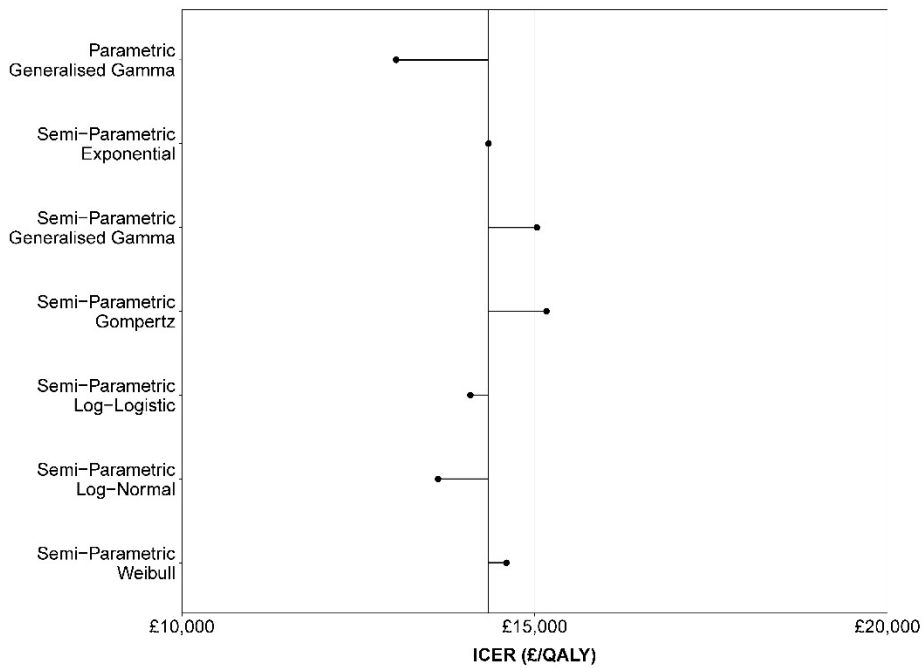
Figure 58. Scenario analysis: impact of alternative NIVO+IPI PFS extrapolations versus FOLFIRI

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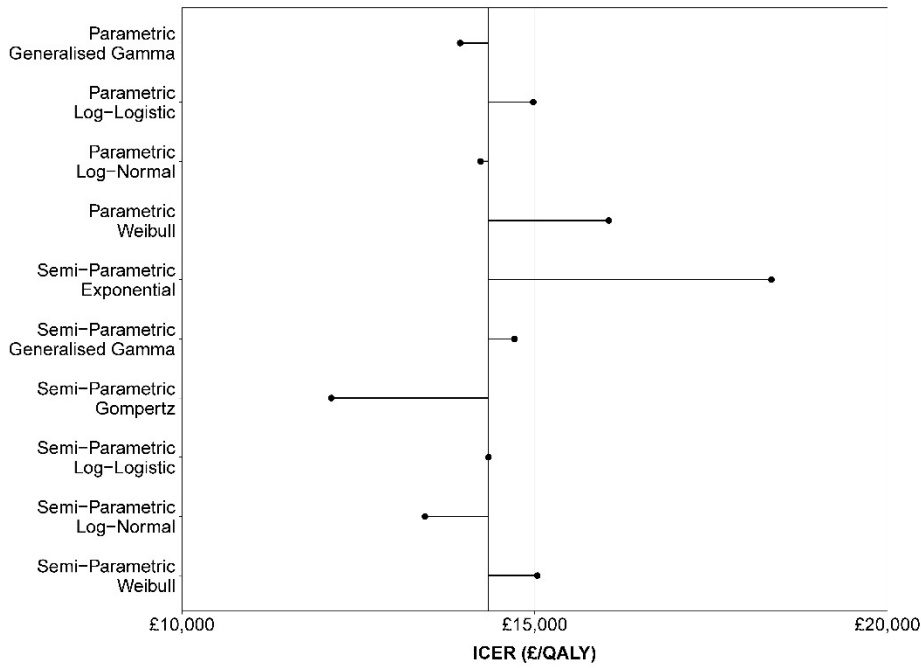
Figure 59. Scenario analysis: impact of alternative NIVO+IPI OS extrapolations versus FOLFIRI
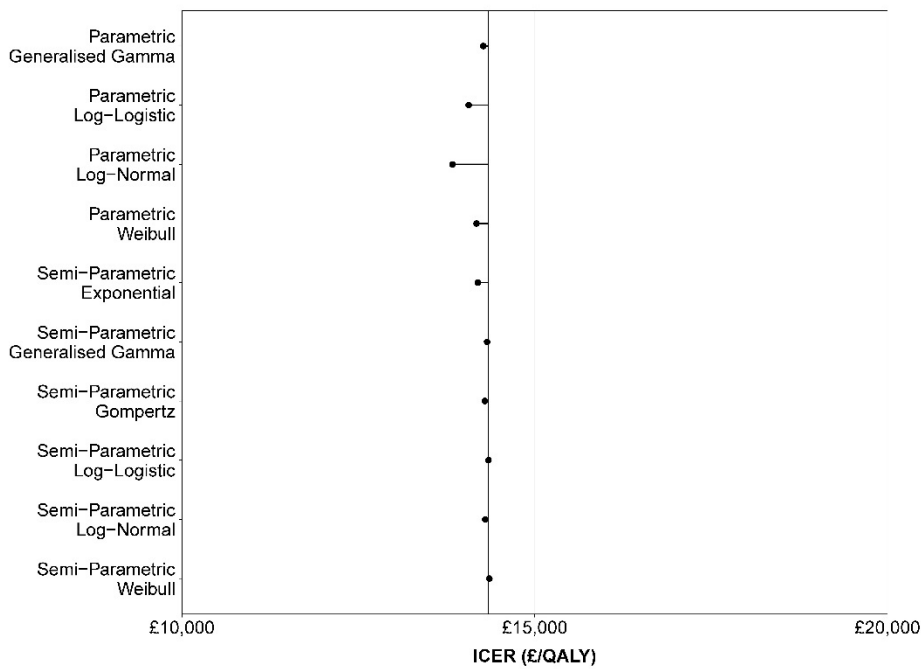
Figure 60. Scenario analysis: impact of alternative NIVO+IPI time on treatment extrapolations versus FOLFIRI

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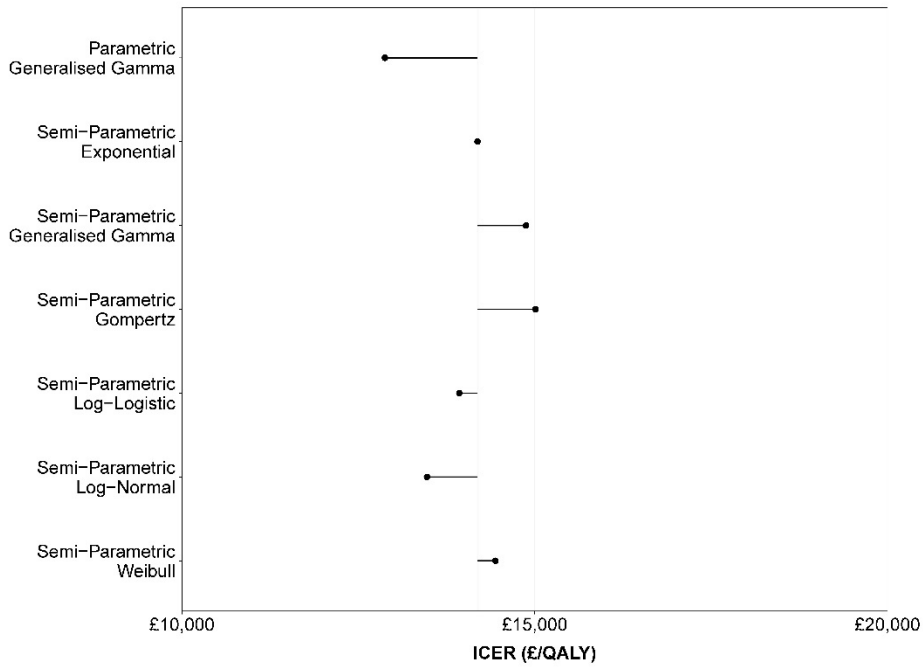
Figure 61. Scenario analysis: impact of alternative NIVO+IPI PFS extrapolations versus irinotecan
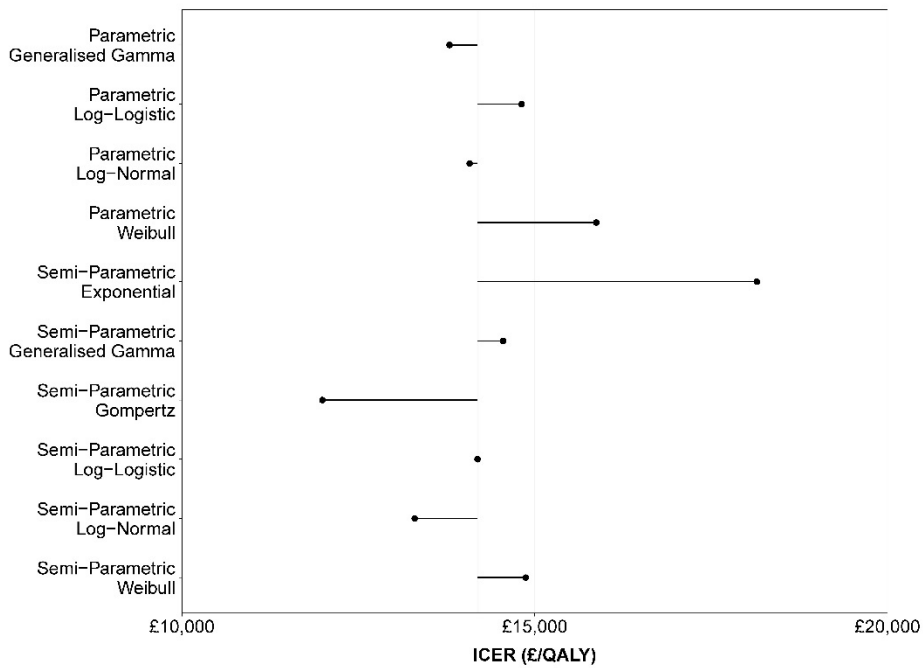
Figure 62. Scenario analysis: impact of alternative NIVO+IPI OS extrapolations versus irinotecan

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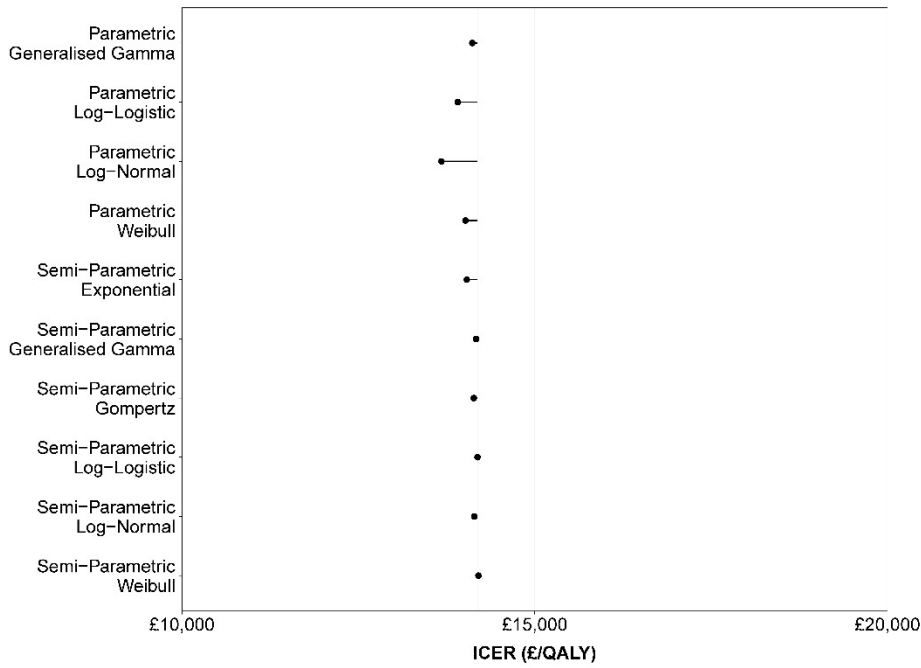
Figure 63. Scenario analysis: impact of alternative NIVO+IPI time on treatment extrapolations versus irinotecan
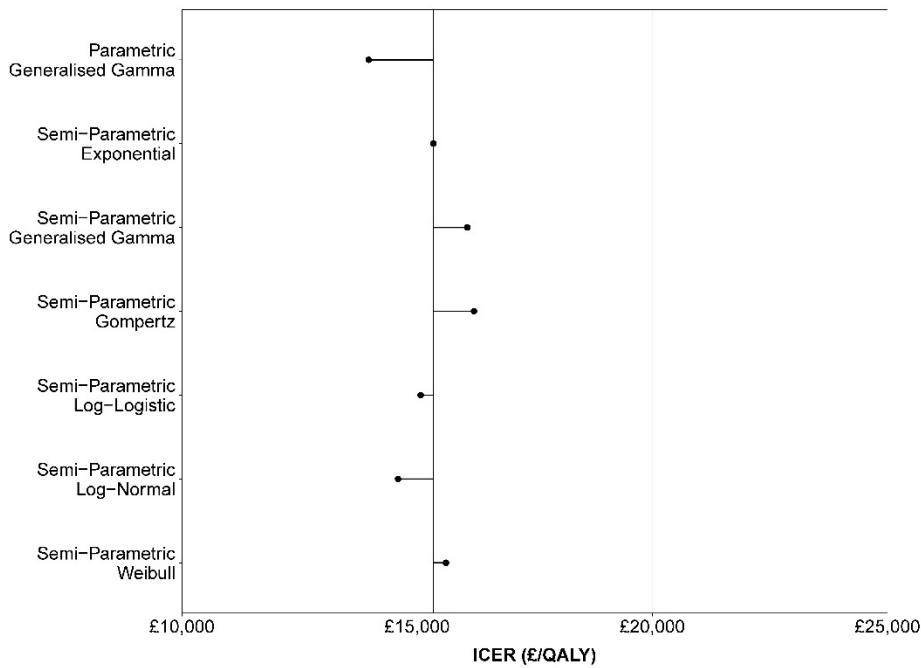
Figure 64. Scenario analysis: impact of alternative NIVO+IPI PFS extrapolations versus raltitrexed

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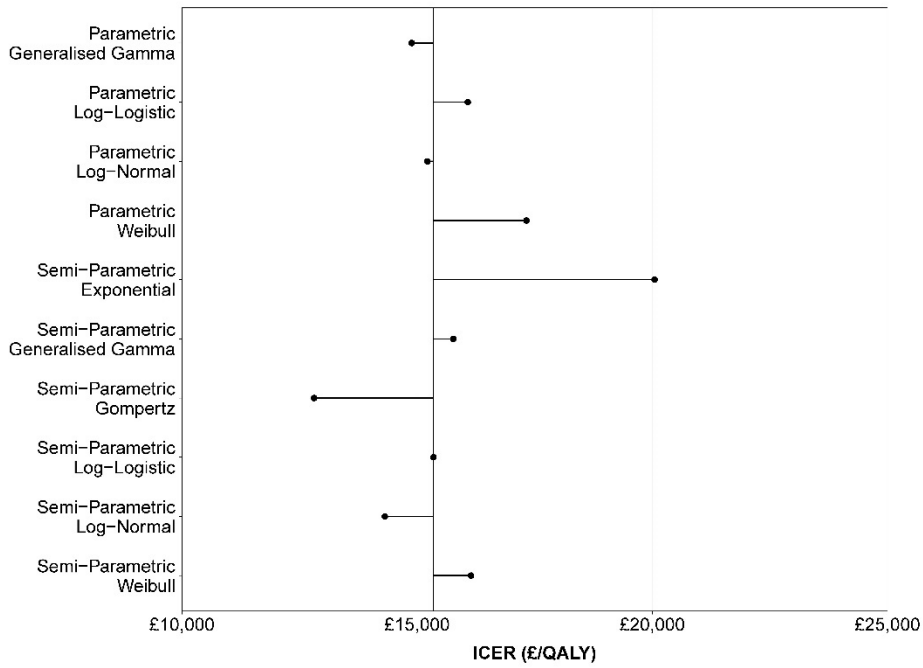
Figure 65. Scenario analysis: impact of alternative NIVO+IPI OS extrapolations versus raltitrexed
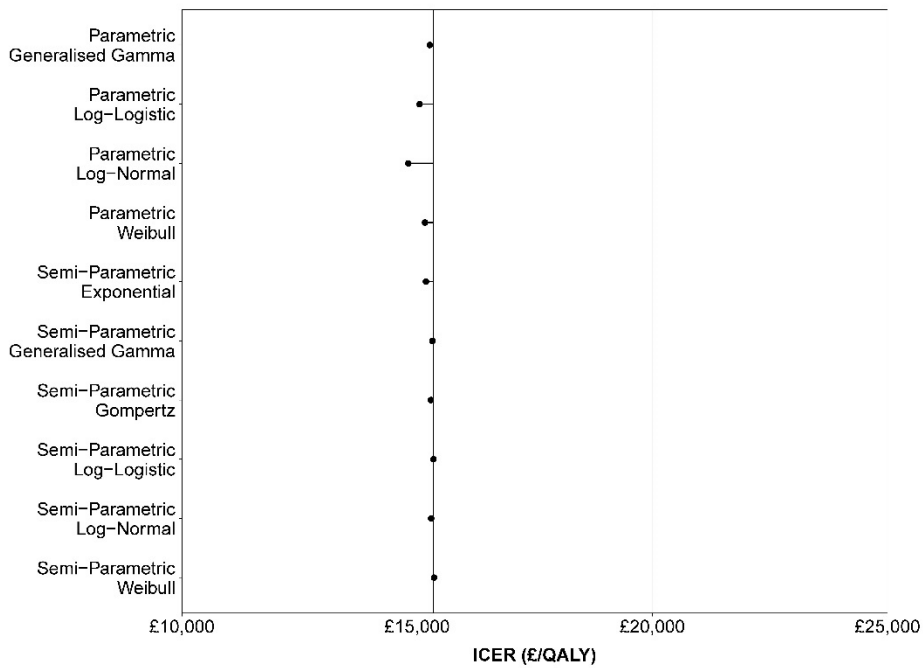
Figure 66. Scenario analysis: impact of alternative NIVO+IPI time on treatment extrapolations versus raltitrexed

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B.3.8.3.3 *Subsequent therapy*

As outlined previously, trifluridine-tipiracil may be a more relevant comparator in patients who are more heavily pre-treated. Hence, patients failing NIVO+IPI, FOLFOX or FOLFIRI may receive trifluridine-tipiracil before progressing to the subsequent therapy observed in TA405. As a scenario analysis, this treatment sequence was modelled to assess the impact, applying trifluridine-tipiracil costs based on mean time on treatment observed during RECOURSE.

Results from the analysis is detailed in Table 59, with ICER estimates of £14,526 per QALY versus FOLFOX and £14,613 per QALY versus FOLFIRI. It should be noted that both ICERs decrease versus the base case analysis. This can be expected, as subsequent therapy is applied on discontinuation, which happens earlier for comparators than for NIVO+IPI, so that discounting has a greater effect. Further, trifluridine-tipiracil is slightly more expensive therapy than BSC and is applied for a short time, so there is limited effect associated with longer life expectancy in NIVO+IPI patients.

Table 59. Scenario analysis: impact of applying subsequent therapy costs

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	£16,510	1.258	0.884	■	■	■	**£14,526**
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£18,889	1.231	0.874	■	■	■	**£14,613**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PSA: probabilistic sensitivity analysis; QALYs, quality-adjusted life years							

B.3.8.3.4 *Alternative sources of comparator efficacy*

The base case analysis applies the best available evidence, which is the outcomes of MAIC analyses applying the reduced set of clinically relevant covariates. However, a series of scenario analyses has been conducted assessing the impact of applying alternative efficacy evidence, as described in Table 60. These analyses include:

- Alternative MAIC analyses not used in the base case analysis. This is only relevant for comparator treatments with alternative sources of data (i.e. trifluridine-tipiracil, BSC, FOLFIRI and irinotecan).

- An unadjusted analysis: based on combining comparator data from the SLR using standard meta-analysis techniques. These survival outcomes include data derived from Kaplan-Meier data, median survival and survival at outcomes. Further, these outcomes are not combined based on relative measures versus CheckMate 142.

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- A pooled set of outcomes: based on the weighted mean of outcomes reported in the SLR. In this analysis, survival outcomes are derived from reported median survival data, and do not include outcomes derived from survival at time points or Kaplan-Meier data. Further, these outcomes are not combined based on relative measures versus CheckMate 142 but are instead simply weighted by study size. This limits the number of calculations, assumptions and inferences required to provide comparisons.

Results from the analysis is detailed in Table 61 to Table 63, with ICER estimates ranging from £13,304 per QALY (unadjusted survival outcomes, versus trifluridine-tipiracil) to £15,265 per QALY (pooled survival outcomes, versus FOLFIRI). Although there are slight variations versus the base case analysis, cost-effectiveness conclusions remain unchanged.

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Table 60. Measures of comparator efficacy

Scenario	Mean outcome (months)	Trifluridine-tipiracil	BSC	FOLFOX	FOLFIRI	Irinotecan	Raltitrexed
Base case	PFS	4.2	2.1	4.5	6.3	6.7	8.6
	OS	10.9	7.6	15.6	15.3	15.4	20.4
Alternative sources of comparator data	PFS	3.7	1.9	NR	7.5	3.8	NR
	OS	11.7	8.1	NR	17.2	13.3	NR
Unadjusted survival outcomes	PFS	3.6	1.8	5.5	6.8	5.6	4.0
	OS	10.4	7.2	17.3	15.7	14.6	8.5
Pooled survival outcomes (medians)	PFS	2.6	1.7	4.9	4.6	3.5	2.4
	OS	7.9	6.1	11.9	12.7	10.4	6.3
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; IPI: ipilimumab; NR: not reported; OS: overall survival; PFS: progression-free survival							

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Table 61. Scenario analysis: impact of using alternative sources for comparator survival

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£17,246	0.953	0.672	■	■	■	£13,418
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	£9,636	0.672	0.472	■	■	■	£14,240
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£11,689	1.375	0.978	■	■	■	£15,183
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
Irinotecan	£11,253	1.078	0.758	■	■	■	£14,673
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; PSA: probabilistic sensitivity analysis; QALYs, quality-adjusted life years							

Table 62. Scenario analysis: impact of using unadjusted survival outcomes for comparator survival

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,973	0.850	0.602	■	■	■	£13,304
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	£9,303	0.599	0.422	■	■	■	£14,177
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	£12,334	1.384	0.975	■	■	■	£15,056
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£11,525	1.261	0.898	■	■	■	£14,993
Comparison E							
NIVO+IPI	■	■	■	-	-	-	-
Irinotecan	£11,179	1.175	0.833	■	■	■	£14,882
Comparison F							
NIVO+IPI	■	■	■	-	-	-	-
Raltitrexed	£11,885	0.702	0.503	■	■	■	£13,937
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years							

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Table 63. Scenario analysis: impact of using pooled outcomes for comparator survival

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£17,168	0.928	0.656	■	■	■	**£13,393**
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	£9,756	0.719	0.507	■	■	■	**£14,305**
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	£12,023	1.375	0.976	■	■	■	**£15,117**
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£12,094	1.464	1.034	■	■	■	**£15,265**
Comparison E							
NIVO+IPI	■	■	■	-	-	-	-
Irinotecan	£11,383	1.213	0.856	■	■	■	**£14,906**
Comparison F							
NIVO+IPI	■	■	■	-	-	-	-
Raltitrexed	£12,140	0.750	0.533	■	■	■	**£13,964**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years							

B.3.8.3.5 *Impact of applying BICR-assessed PFS*

Within the base case analysis, progression and response are applied based on investigator-assessed endpoints from clinical studies, as clinical experts suggest that this is likely to reflect clinician behaviour in a real-world setting. Similarly, this may better reflect the accrual of costs and QALYs of mCRC patients, as a patient considered not to have progressed by the clinician is likely to have a different quality of life and management plan compared with a patient considered to have progressed. Similar to the base case analysis, an exponential fit was deemed appropriate to capture the progression-free survival.

Results from the analysis is detailed in Table 64, with ICER estimates ranging from £13,405 per QALY (versus trifluridine-tipiracil) to £15,387 per QALY (versus raltitrexed).

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**Table 64. Scenario analysis: impact of using BICR-assessed PFS for NIVO+IPI**

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■	■	■	**£13,405**
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	£9,379	0.626	0.441	■	■	■	**£14,248**
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	£12,176	1.258	0.884	■	■	■	**£14,879**
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£11,527	1.231	0.874	■	■	■	**£14,970**
Comparison E							
NIVO+IPI	■	■	■	-	-	-	-
Irinotecan	£11,139	1.240	0.883	■	■	■	**£15,062**
Comparison F							
NIVO+IPI	■	■	■	-	-	-	-
Raltitrexed	£13,389	1.616	1.147	■	■	■	**£15,387**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years							

B.3.8.3.6 *Impact of removing stopping rules*

This scenario explores the impact of the removal of the 2-year stopping rule.

Results from the analysis are detailed in Table 65, where removing the stopping rule resulted in ICER estimates ranging from £31,655 per QALY (versus trifluridine-tipiracil) to £35,165 per QALY (versus raltitrexed).

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**Table 65. Scenario analysis: impact of applying no stopping rule to patients in the NIVO+IPI arm**

| Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■	■	■	**£31,655**
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	£9,379	0.626	0.441	■	■	■	**£31,907**
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	£12,176	1.258	0.884	■	■	■	**£33,814**
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£11,527	1.231	0.874	■	■	■	**£33,869**
Comparison E							
NIVO+IPI	■	■	■	-	-	-	-
Irinotecan	£11,139	1.240	0.883	■	■	■	**£33,982**
Comparison F							
NIVO+IPI	■	■	■	-	-	-	-
Raltitrexed	£13,389	1.616	1.147	■	■	■	**£35,165**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years							

B.3.8.3.7 *Impact of alternative utilities*

Given the uncertainty in application of treatment-specific utilities, values from the published literature were assessed in scenario analysis, wherein NIVO+IPI utility values were assumed as per comparators and applied by progression status, as opposed to treatment status, as in the base case.

Results from the analysis is detailed in Table 66, where the impact of applying equal utility values between arms resulted in ICER estimates ranging from £13,148 per QALY (versus trifluridine-tipiracil) to £15,070 per QALY (versus raltitrexed).

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Table 66. Scenario analysis: impact of applying equal utility value between arms

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■■	■■	■■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■■	■■	■■	£13,148
Comparison B							
NIVO+IPI	■■	■■	■■	-	-	-	-
BSC	£9,379	0.626	0.441	■■	■■	■■	£13,985
Comparison C							
NIVO+IPI	■■	■■	■■	-	-	-	-
FOLFOX	£12,176	1.258	0.884	■■	■■	■■	£14,585
Comparison D							
NIVO+IPI	■■	■■	■■	-	-	-	-
FOLFIRI	£11,527	1.231	0.874	■■	■■	■■	£14,675
Comparison E							
NIVO+IPI	■■	■■	■■	-	-	-	-
Irinotecan	£11,139	1.240	0.883	■■	■■	■■	£14,765
Comparison F							
NIVO+IPI	■■	■■	■■	-	-	-	-
Raltitrexed	£13,389	1.616	1.147	■■	■■	■■	£15,070
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years							

B.3.8.3.8 Impact of inclusion of testing for MSI test cost

As noted in the final scope, current NICE guidance recommends that all people with colorectal cancer should be offered testing when first diagnosed, using immunohistochemistry for mismatch repair proteins or MSI testing to identify tumours with dMMR.[2, 3] This was based on economic evaluations conducted as part of Diagnostics Guidance 27 [DG27].[3] Further, NG151 notes that testing for dMMR may inform systemic therapy choices for those with non-metastatic colorectal cancer, but the NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer already recommends such testing for all people with colorectal cancer when first diagnosed.[4] For this reason no further recommendations were made about testing for deficient DNA mismatch repair.

This assumption is validated by clinical experts, who note that this is an easy test to carry out and that all patients should be tested given it is in the NICE guidance. In particular, given that immuno-oncology therapies are available for this group, testing for this MSI high status is even more important.[1]

Further, this is in line with ERG comments on an ongoing mCRC appraisal (ID1598), where it was noted that test for BRAF status is "recommended in the updated NICE guideline (NG151)

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for all patients with mCRC at first diagnosis to help guiding the selection of systemic anti-cancer therapy. Consequently, the test is becoming a standard care and does not present an incremental cost compared with comparators for the use of the technology."[4]

However, in order to provide evidence relevant to the final scope, a scenario analysis was undertaken assessing the impact of the cost of MSI-H/dMMR testing. The cost of MSI testing was derived from the cost of immunohistochemistry from DG27. [3] Although this testing will be undertaken in the majority of patients, in line with DG27[3], a conservative approach was taken and it was assumed that no patients would receive this test in the comparator arm. This cost was applied at model initiation in the NIVO+IPI arm.

Results from the analysis is detailed in Table 67, where the impact of including a cost for MSI-H test resulted in ICER estimates ranging from £13,405 per QALY (versus trifluridine-tipiracil) to £15,387 per QALY (versus raltitrexed), with minimal increases in the ICER compared to the base case.

Table 67. Scenario analysis: impact of including cost for testing for MSI

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■	■	■	**£13,405**
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	£9,379	0.626	0.441	■	■	■	**£14,248**
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	£12,176	1.258	0.884	■	■	■	**£14,879**
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£11,527	1.231	0.874	■	■	■	**£14,970**
Comparison E							
NIVO+IPI	■	■	■	-	-	-	-
Irinotecan	£11,139	1.240	0.883	■	■	■	**£15,062**
Comparison F							
NIVO+IPI	■	■	■	-	-	-	-
Raltitrexed	£13,389	1.616	1.147	■	■	■	**£15,387**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years							

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B.3.8.3.9 *Remission in a proportion of patients*

Some UK clinical experts asserted that long-term outcomes were very good in patients who were alive and pre-progression in two years. These experts described these patients as being in remission, with only a small proportion subject to ongoing hazard from CRC-related death.

In line with this suggestion, an analysis was undertaken wherein 90% of patients who are alive and pre-progression at two years are assumed to be subject to general population survival and utility.

Results from the analysis is detailed in Table 68, where the impact of including a mixture/cure proportion resulted in ICER estimates ranging from £9,615 per QALY (versus trifluridine-tipiracil) to £10,756 per QALY (versus raltitrexed), with significant changes in incremental QALY benefit driving the reduced ICERs.

Table 68. Scenario analysis: impact of including mixture/cure proportion

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■	■	■	£9,615
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	£9,379	0.626	0.441	■	■	■	£10,320
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	£12,176	1.258	0.884	■	■	■	£10,548
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£11,527	1.231	0.874	■	■	■	£10,619
Comparison E							
NIVO+IPI	■	■	■	-	-	-	-
Irinotecan	£11,139	1.240	0.883	■	■	■	£10,680
Comparison F							
NIVO+IPI	■	■	■	-	-	-	-
Raltitrexed	£13,389	1.616	1.147	■	■	■	£10,756
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years							

B.3.9. *Summary of sensitivity analysis results*

A large number of sensitivity analyses have been undertaken, assessing the impact of variation in all variables and assumptions applied within the model. In the deterministic analysis, NIVO+IPI was cost-effective against all scenarios at a WTP threshold of

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£50,000/QALY. Similarly, in the PSA, the probability that NIVO+IPI is cost-effective versus trifluridine-tipiracil, BSC, FOLFOX, FOLFIRI and irinotecan is ██ and ██ versus raltitrexed at a WTP threshold of £50,000/QALY.

Plausible alternative inputs and assumptions were assessed as scenario analyses within Section B.3.8.3, as depicted in Figure 67. Reflecting the PSA and deterministic sensitivity analysis, all of the ICERs remain below the £50,000/QALY threshold.
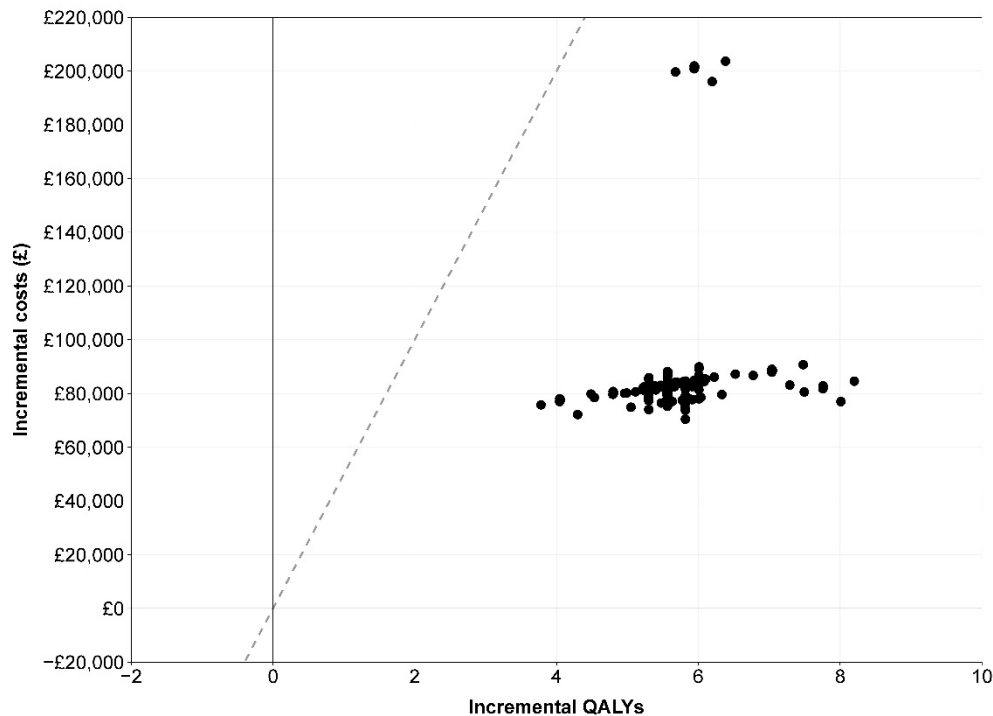
Figure 67. Scenario analysis: overview of all scenarios
Dotted line represents the willingness-to-pay threshold of £50,000 per QALY

B.3.10. Subgroup analysis

All available subgroup analyses are provided in Section B.3.8.3.

B.3.11. Validation

B.3.11.1. Validation of cost-effectiveness analysis

In the specific context of previously treated dMMR/MSI-H mCR, there are low patient numbers and poor survival outcomes. Hence, there is a distinct paucity of evidence describing clinical practice on which to base economic evaluation. In general, where no evidence has been

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identified, simple assumptions have been made based on independent sources, such as published literature, CRC guidelines or previous NICE appraisals in the field of CRC. These assumptions were then assessed for clinical plausibility; uncertainty has been characterised through the use of sensitivity analyses. Extensive sensitivity analyses were then undertaken, and all ICERs remain below a £50,000/QALY threshold.

A technical review of the cost-effectiveness model was conducted by an independent economist. Further, the relevance of the model structure and assumptions were validated through consultation with UK clinicians. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

B.3.11.2. Validation of nivolumab plus ipilimumab survival extrapolation

Despite the lack of real-world data, it was possible to validate the survival extrapolation for NIVO+IPI against longer-term survival data from other indications. Available long-term data is presented in Table 69. As can be seen, immunotherapy studies typically exhibit a higher rate of mortality followed by a lower rate of mortality over long-term follow-up. Additionally, long term survivorship without the need for prolonged treatment has been observed for immunotherapies in other indications. For example, ipilimumab therapy administered for four cycles at three-weekly intervals can lead to ten-year survival in 20-25% of melanoma patients, as presented in Figure 68.[106]

Available Kaplan-Meier data from the CheckMate 142 trial indicates that the OS in dMMR/MSI-H mCRC will be high in patients receiving NIVO+IPI. At two years, OS is ▮▮, which is higher than was observed for other indications. By contrast, long-term follow-up for other indications indicates more patients survive into 5 years and 10 years than is predicted by the extrapolations applied in this submission, with most studies demonstrating a survival plateau as depicted in Figure 68. If a similar plateau in OS is observed in the CheckMate 142 study upon maturation of the data, the model used to extrapolate the OS data in the base case analysis would provide a conservative estimate of the long-term survival benefit associated with NIVO+IPI. It should be noted that alternative survival extrapolations did not impact greatly on cost-effectiveness outcomes. Further, a threshold analysis was undertaken to assess the impact of any survival extrapolation uncertainty.

B.3.11.2.1 Expert validation of survival extrapolation

The survival modelling approach was presented to UK clinicians, in order to provide validation. Clinicians were surprised not to observe more of a plateau effect in the extrapolations, given the observed evidence. However, they considered that the survival extrapolations to be a plausible conservative estimation of outcomes.

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Additionally, this approach to modelling survival was undertaken with reference to the guidance from the NICE Decision Support Unit (DSU)[112] and Bagust and Beale (2014)[113] within the context of only using single-arm data.
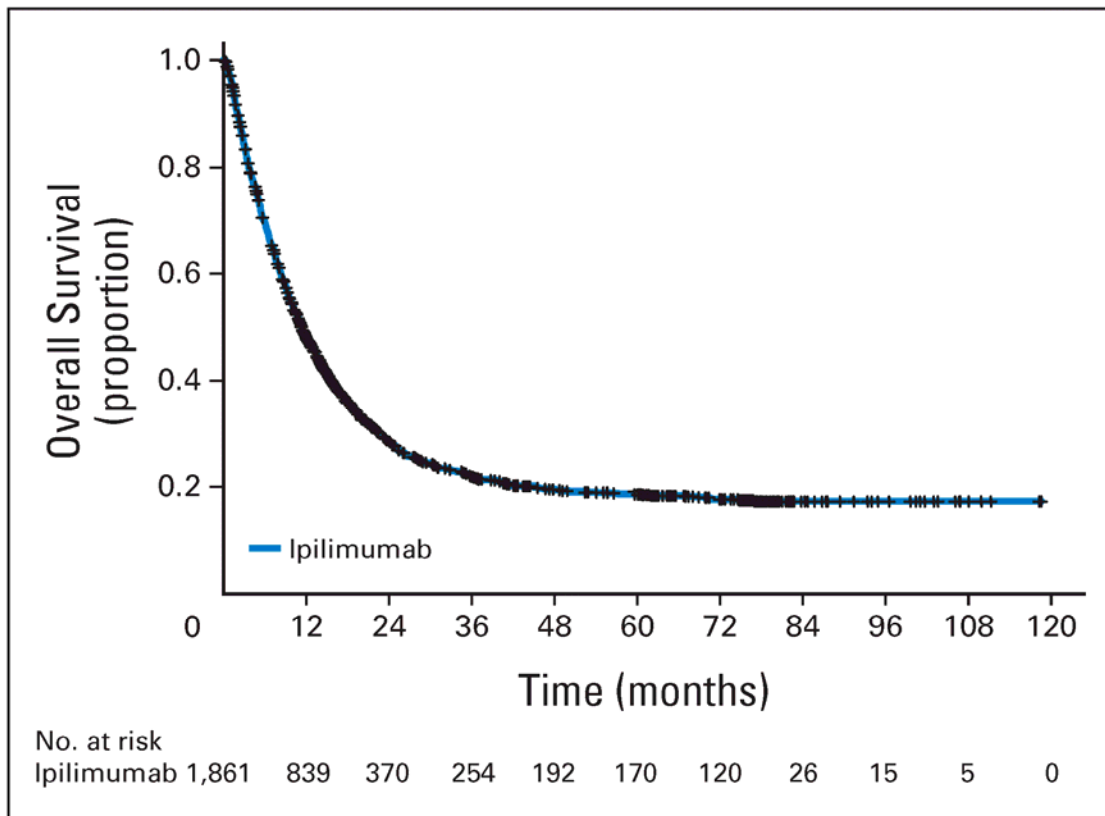
Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

Figure 68. Overall survival following ipilimumab therapy in metastatic melanoma (presented as figure 1 in Schadendorf et al 2015[106])

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Table 69. Survival rates for immunotherapies with available long-term follow-up

Study	CheckMate 142	CheckMate 025	CheckMate 017/057	CheckMate 017/057/063/003	CheckMate 003	Schadendorf et al., 2015[106]	CheckMate 067
Reference		Plimack et al., 2016[149]	Vokes 2018[150], Gettinger 2019[151]	Antonia 2019	Hodi et al., 2016[152]		Hodi 2018[153], Wolchok 2017[154], Larkin 2019[107]
Drug	Nivolumab + ipilimumab	Nivolumab	Nivolumab	Nivolumab	Nivolumab	Ipilimumab	Nivolumab plus ipilimumab
Indication	dMMR/MSI-H mCRC	RCC	NSCLC	NSCLC	Melanoma	Melanoma	Melanoma
n	■	410	427	664	107	1,861	314
12 month OS	■	76%	48%		63%	~27%	73%
24 month OS	■	52%	27%		48%	~47%	64%
36 month OS	■	~35%	17%		42%	22%	58%
48 month OS	■	-	-		35%	~21%	-
60 month OS	■	-	13.4%	14%	34%	~20%	-
120 month OS	■	-	-		-	~18%	52%

ACM: all cause mortality; NSCLC: non-small cell lung cancer; OS: overall survival; RCC: renal cell carcinoma
~ numbers approximated from visual inspection of Kaplan Meier curves

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B.3.11.2.2 *Exploration of survival extrapolation techniques for cancer immunotherapy*

Limited clinical trial follow-up and low event rates for survival endpoints introduce uncertainty in survival extrapolation for immunotherapies. Traditional conservative approaches can adversely impact estimates of cost-effectiveness, impacting on HTA outcomes as well as restricting patients' access to these medicines. There is also growing evidence that parametric survival models may be unable to capture the characteristic plateau observed in the latter period of immunotherapy survival curves, as well as to model hazard functions with multiple inflection points.[155-158]

To examine this problem, two case studies have been undertaken to assess a range of extrapolation methods to patient-level survival data to assess their predictive accuracy over time. Multiple extrapolation methods were examined:

███
███
████████████████. Data from two separate studies were assessed:

- CheckMate 067: Phase III randomised controlled study that compared PFS and OS of nivolumab monotherapy and NIVO+IPI versus ipilimumab monotherapy in patients with previously untreated, unresectable or metastatic melanoma, using data cuts at ████████████████████████████████████

- CheckMate 025: Phase III randomised controlled trial comparing nivolumab with everolimus for previously treated advanced renal cell carcinoma, using data cuts at ████████████████████████████████████

The extrapolation models were fitted to the earlier database locks and NICE DSU 14 was used to inform model selection. The extrapolations for each model were compared with the observed data from the latest database locks.

In the CheckMate 025 case study, ███
███
███
███
████████████████████████████████

In the CheckMate 067 case study, ███
███
███
███
████████████████

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In a similar study, survival modelling from TA319 (ipilimumab in melanoma) was revisited to assess the accuracy of extrapolation methods.[158] In addition to the piecewise survival model used in TA319, alternative models were assessed (fit to trial data with minimum follow-up of 3 years), including parametric, spline-based, mixture, and mixture-cure models. These were compared against a longer-term data cut (5-year follow-up). Only the survival model used in TA319 and a mixture-cure model provided 5-year survival predictions close to those observed in the 5-year follow-up data set. Standard parametric, spline, and non–curative-mixture models substantially underestimated 5-year survival.[158]

Based on this evidence, it can be concluded that estimating long-term survival for NIVO+IPI through piecewise Kaplan-Meier and extrapolation may underestimate the long-term survival benefit of this therapy, and the current estimates may be considered conservative.

B.3.11.3. Comparison of outputs with TA405

TA405 provides outputs for trifluridine-tipiracil , although these outputs apply a PAS discount to costs.[2] A comparison of outputs for trifluridine-tipiracil versus TA405 is provided in Table 70. As can be seen, predicted LYs are broadly comparable with values output from TA405. Predicted costs are also comparable with the difference potentially due to the impact of the price fluctuations during the intervening period. QALY outcomes have slightly more variation than those produced during TA405. However, this may be due to slight differences in PFS and OS outcomes as a result of the MAIC, as application of naïve outcomes from RECOURSE (Table 62) produced an equivalent absolute QALY value (0.602 versus 0.59 and 0.54).

Table 70. Comparison of outcomes for trifluridine-tipiracil

	Current appraisal	TA405[2]	
		Company	ERG
Costs	£16,981	£16,386*	£17,167*
QALYs	0.630	0.59	0.54
LYs	0.915	0.92	-
* applies PAS for trifluridine-tipiracil			

B.3.11.4. Rationale for observed post-progression survival outcomes

As outlined in Table 50, mean PFS in the NIVO+IPI arm is predicted to be ▇▇ years, while post-progression survival is predicted to be ▇▇▇ years. Although this can be considered to be unusual, long post-progression survival can be considered plausible in the context of the available data.

In particular, the PFS extrapolation applied in the base case analysis (semi-parametric exponential function) can be considered conservative, with the log-logistic and lognormal function providing equally plausible fits to the data but vastly increased predictions of PFS. Use of these extrapolations improve the ICER slightly and extends mean PFS predictions to ▇▇▇▇▇ years, which provides more plausible estimates of post-progression survival (▇▇▇▇ years). To note, these alternative extrapolations had minimal impact on the ICER.

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Further, it should be noted that 20 of the 40 patients who progressed on NIVO+IPI continued on their initial study treatment following progression. Clinicians validated this observation, noting that patients experiencing early progression frequently will respond following progression and will go on to achieve long lasting benefits. Hence, there is strong rationale that the PFS data is underestimating the benefit of NIVO+IPI.

In support of this evidence, an analysis of observed post-progression survival was undertaken. As can be seen in Figure 69, a significant proportion of patients experiencing a progression event subsequently achieve long-term survival, indicating that a post-progression benefit would be plausible.

Figure 69. CheckMate 142: comparison of pre-progression survival and post-progression survival (investigator-assessed endpoints; censored for subsequent treatments)

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B.3.12. Interpretation and conclusion of economic evidence

Base case analysis

- Use of NIVO+IPI results in an increased mean OS ranging from ▉▉ years (versus raltitrexed) to ▉▉ years (versus BSC), as well as additional discounted QALYs and life years of up to ▉▉ and ▉▉, respectively.

- Discounted incremental costs were estimated to be ▉▉▉–▉▉▉ under base case assumptions and the resultant ICERs were £13,367-£15,346 per QALY, which are considered to be cost-effective at a willingness-to-pay threshold of £50,000 per QALY.

Sensitivity analysis

- In the probabilistic sensitivity analysis and deterministic sensitivity analysis, NIVO+IPI was cost-effective in all scenarios at a willingness-to-pay threshold of £50,000 per QALY.

- Extensive scenario analyses were undertaken, reflecting the assumptions required to undertake plausible, robust and transparent base case analysis. Within these scenario analyses, all of the ICERs remain below the £50,000 per QALY threshold

- Therefore, NIVO+IPI can be considered a cost-effective use of NHS resources.

In the specific context of ▉▉, there are low patient numbers with poor survival outcomes. Therefore, there is a distinct paucity of evidence describing clinical practice on which to base economic evaluation. In general, where no evidence has been identified, simple assumptions have been made based on independent sources, such as published literature, CRC guidelines or previous NICE appraisals in the field of CRC. These assumptions were then assessed for clinical plausibility; uncertainty has been characterised through the use of sensitivity analyses and rationales for each assumption are provided in Section B.3.6.2. Extensive sensitivity analyses were then undertaken, and all of the ICERs remained below the £50,000/QALY threshold.

As previously noted, this analysis has been designed to be comparable with previous health economic analysis and HTAs in CRC, facilitating review and transparency. Further, the approach has been chosen to reflect the most important treatment outcomes for most CRC patients: survival (progression free and overall), side effects and quality of life.

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In the base case analysis, it was estimated that NIVO+IPI use would result in an additional ▮▮▮▮▮ discounted QALYs and ▮▮▮▮▮▮ undiscounted life years versus comparators of interest. Further, it was estimated that patients receiving NIVO+IPI would spend ▮▮ years in the pre-progression state (versus 0.185-0.729 for patients receiving comparator treatments), with a subsequent ▮▮▮ years in the post-progression state (versus 0.455-0.981 years for comparators), indicating a substantial benefit to survival in both the pre- and post-progression period. Discounted incremental costs were expected to range between ▮▮▮ (versus trifluridine-tipiracil) to ▮▮▮ (versus BSC) under base case assumptions and the resultant ICERs ranged from £13,366 (versus trifluridine-tipiracil) to £15,346 (versus raltitrexed), which means all comparison can be considered cost-effective at a willingness-to-pay threshold of £50,000/QALY.

The case for application of NICE end-of-life criteria is set out in Table 20, and based on this evidence, it can be considered that NIVO+IPI meets both criteria for end-of-life. This was supported by clinicians consulted for this submission, who emphasised explicitly that they would expect NIVO+IPI to qualify for end-of-life, given the short life expectancy of previously treated dMMR/MSI-H mCRC and the significant survival benefit NIVO+IPI is expected to provide compared to standard of care.[1]

In summary, availability of NIVO+IPI would provide an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need. The adoption of NIVO+IPI in this therapeutic indication in NHS England would represent a further, significant advance in the management of this life-threating condition and would be a cost-effective use of NHS resources.

B.3.12.1. Application of NICE end of life criteria to nivolumab plus ipilimumab use in mCRC MSI-H

End of life criteria as applied by NICE are summarised as follows:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months; and

- There is sufficient evidence to indicate that the treatment offers an extension to life of at least 3 months versus current standard of care in the NHS.

Current standard of care for the mCRC overall population is associated with poor outcomes; estimates of median OS were low (with weighted mean median OS ranging from 6.05-12.73 months for comparators) based on SLR evidence for ▮▮▮, and a previous NICE appraisal in this patient population has noted that life expectancy is likely to be less than 24 months.[2] NIVO+IPI has a one-year OS rate of ▮▮▮, which is significantly higher than for comparators (weighted mean of reported values: 34.91%; range: 0-69.5%). The weighted mean of reported

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values was 9.48 months for median OS, while median OS for NIVO+IPI was not reached despite ███████████████. Additionally, based on the ITC presented in Section B.2.9.2 the estimated mean OS for NIVO+IPI is around ██████████, while comparator mean OS ranged from 7.22 months to 20.41 months. A comparison of CheckMate 142 with outcomes from the overall mCRC population may be considered conservative, as outcomes may be poorer in mCRC patients with MSI-H/dMMR status. However, despite the potential underestimation of benefit, the benefit is still demonstrated to exceed 3 months.

Further, clinicians consulted for this submission highlighted that there are very few patients in this population (only ~4% of the mCRC are MSI-high), and that outcomes are even worse than in the overall population. Therefore, a high degree of unmet medical need remains for effective and tolerable treatments for this patient population

The case for application of NICE end-of-life criteria is set out in Table 20, and based on this evidence, it can be considered that NIVO+IPI meets both criteria for end-of-life. This was supported by clinicians consulted for this submission, who emphasised explicitly that they would expect NIVO+IPI to qualify for end-of-life.[1]

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Appendices

List of appendices

In line with the user guide for company evidence submission template, appendices start at C, because document A is the submission summary and document B is the main submission.

Appendix number	Appendix Title	Location
C	Nivolumab SmPC NB: A version of the European public assessment report or scientific discussion is not yet available	Provided as a separate document
D	Identification, selection and synthesis of clinical evidence: systematic literature review report	Provided as a separate document
E	Subgroup analysis	Provided in the main body of the report
	E.1: CheckMate 142 Clinical Study Report	Provided as a separate document
	E.2: CheckMate 142 Clinical Study protocol	Provided as a separate document
F	Adverse reactions	Provided in the main body of the report
G	Published cost-effectiveness studies: systematic literature review	Provided as a separate document
H	Health-related quality-of-life studies: systematic literature review	Provided as a separate document
I	Cost and healthcare resource identification:	Provided as a separate document
J	Clinical outcomes and disaggregated results from the model	Provided in the main body of the report
K	Checklist of confidential information	Provided as a separate document
L	Indirect treatment comparison report	Provided as a separate document
M	Survival analysis report	Provided as a separate document
N	Utility analysis report	Provided as a separate document

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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]

Clarification questions

November 2020

File name	Version	Contains confidential information	Date
ID1332 nivolumab final clarification letter for PM [CIC]	1.0	Yes	26/11/2020

Notes for company

Highlighting in the template

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

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

Updated outcomes from CheckMate 142

Following submission, limited outcomes from an updated database lock from CheckMate 142 (Oct 2020) have become available.

In the updated database lock, █ of 119 patients receiving NIVO+IPI had experienced an OS event (Figure 1) demonstrating that OS outcomes are ████████████████████████████, with median OS ████████████. Similarly, only █ patients had experienced a PFS event (per investigator [Figure 2] and per BICR [Figure 3]), so that median PFS was ████████ per investigator and was ████████ per BICR.

These outcomes surpass previously reported data and support the beneficial impact of NIVO+IPI in previously treated patients with MSI-H/dMMR mCRC.

Figure 1. CheckMate 142 updated overall survival

█

Figure 2. CheckMate 142 updated progression-free survival per investigator

█

Figure 3. CheckMate 142 updated progression-free survival per BICR

█

Figure 4. Comparison of modelled OS extrapolations versus CheckMate 142 updated database lock

█

Figure 5. Comparison of modelled PFS extrapolations versus CheckMate 142 updated database lock

█

Section A: Clarification on effectiveness data

Checkmate 142

A1. What proportion of patients in Checkmate 142 had subsequent therapy prior to progression according to blinded independent central review (BICR) and investigator assessment (IA)?

The proportion of patients who have subsequent therapy prior to progression are detailed in Table 1.

Table 1. CheckMate 142: subsequent treatment prior to progression (Feb 2019 data cut)

	Subsequent treatment prior to progression (Per BICR)	Subsequent treatment prior to progression (Per investigator)

N	119	
Number of events*	■■■■	■■■■
Type of events		
Progression	■■■■	■■■■
Death	■■■	■■■
Subsequent therapy prior to progression		
Number	▮	▮
As proportion of patients with progression events	■■	■■
As proportion of all patients	■■	■■

* Number of events does not align with PFS endpoints events, as patients who initiate a subsequent anticancer treatment prior to progression will be censored at the last evaluable assessment. Hence, patients with subsequent treatments are not reflected in PFS data.

A2. What proportion of patients in Checkmate 142 continued to have nivolumab therapy post progression?

In the Feb 2019 database lock, ■ patients continue to receive nivolumab therapy post progression.[1]

A3. Please provide the number of events, the number of censored patients and the reasons for censoring for progression-free survival (PFS) based on IA and BICR, as well as for overall survival (OS).

Number of events, the number of censored patients and the reason for censoring for progression-free survival (PFS) per BICR and investigator and overall survival (OS) can be found in Table 2, Table 3 and Table 4, respectively.[1]

Table 2. Status of censored patients (Overall survival) – CheckMate 142

	All patients (n=119)
Number of deaths (%)	■■■
Number of patients censored (%)	■■■
Status of censored patients (%)	
Still on treatment	■■■
Not progressed	■■■
Progressed	■■
In Follow-up	■■■
Off study	■■
Lost to follow-up	▮
Patient withdrew consent	■■■
Other	▮

Table 3. Status of censored patients (Progression free survival – BICR assessed) – CheckMate 142

	All patients (n=119)
Number of events (%)	■■■
Type of events (%)	

	Progression		█	
Death			█	
Number of patients censored (%)			█	
Censored on first dosing date (%)			█	
No baseline tumour assessment and no death (%)			█	
No on-study tumour assessment and no death				
Censored on date of last tumour assessment on study (%)			█	
Received subsequent therapy (%)			█	
Still on treatment (%)			█	
Progression-free in follow up (%)			█	
Off study (%)			█	
Lost to follow up (%)				
Patient withdrew consent (%)			█	
Other (%)				

Table 4. Status of censored patients (Progression free survival – investigator assessed) – CheckMate 142

	All patients (n=119)	
Number of events (%)	█	
Type of events (%)		
Progression	█	
Death	█	
Number of patients censored (%)	█	
Censored on first dosing date (%)		
No baseline tumour assessment and no death (%)		
No on-study tumour assessment and no death		
Censored on date of last tumour assessment on study (%)	█	
Received subsequent therapy (%)		
Still on treatment (%)	█	
Progression-free in follow up (%)	█	
Off study (%)		
Lost to follow up (%)		
Patient withdrew consent (%)	█	
Other (%)		

A4. How many patients in Checkmate 142 required hormone replacement therapy as a result of immune-related adverse events?

█ of patients received hormone replacement therapy for adverse event management.[1]

A5. How many patients in Checkmate 142 required treatment with corticosteroids as a result of immune-related adverse events?

█ of patients received corticosteroid for adverse event management.[1]

A6. In Checkmate 142 all adverse events were documented for a minimum of 100 days after the last dose. However, according to the SmPC for nivolumab taken in combination with

ipilimumab adverse events related to the treatments may occur up to 5 months after treatment discontinuation. Please provide the rationale for the 100-day follow-up for safety.

This follow-up time window was recommended by the FDA at the start of the nivolumab program (year 2011).

A7. In the company submission (Document B) it is stated that the maintenance phase of nivolumab alone following nivolumab plus ipilimumab (NIVO+IPI) therapy was given at a dose of 3mg/kg every 2 weeks (Table 7) or a fixed dose of 240mg every 2 weeks (Table 2 and Section B.2.3.3).

   a) **Please confirm which dose of nivolumab participants in CheckMate 142 had for the maintenance phase.**

Patients enrolled in CheckMate 142 received nivolumab 3 mg/kg and ipilimumab 1 mg/kg once every 3 weeks for four doses and then nivolumab 3 mg/kg IV once every 2 weeks.[2, 3] This equates to 221.1 mg assuming body weight of 73.7 kg, based on mean weight in CheckMate 142. As nivolumab vials provide a dose of 240mg, it is assumed that the remainder of each vial is wasted.

Table 2 in the company submission refers to the dosage included in the market authorisation application, which includes a fixed dose of 240mg every 2 weeks.

   b) **The ERG notes that the company has received marketing authorisation for a fixed dose of nivolumab for the monotherapy phase of 480mg every 4 weeks for melanoma and renal cell carcinoma. Please can the company confirm whether they are applying for marketing authorisation at this dosage for this indication?**

The company will be applying for marketing authorisation at the fixed dose of 240mg every 2 weeks.

A8. Please clarify the discrepancy in Lam 2020 RWE data. In the text median PFS is reported as 8.3 months and 16.7 months for nivolumab and NIVO+IPI, respectively. Figure 22, on the other hand indicates that median PFS is roughly 9 months for nivolumab monotherapy but not reached for NIVO+IPI.

This publication reports on findings of a real-world evidence study conducted by the University College London Hospital.[4] We are currently following up on the discrepancy between the reported results and the poster figure and will get back as soon as possible.

A9. Please provide a discussion of the difference between the results of CheckMate 142 (IA median PFS 41.5 months) and the Lam 2020 RWE data (median PFS either 16.7 months according to the text or not reached, according to Figure 22).

It is always challenging comparing clinical trials and real-world evidence. Lam 2020 was a small real world study conducted in the UK, based on 49 patients of whom only 12 received NIVO+IPI.[4] While these results are broadly supportive of the positive impact of NIVO+IPI, it is not possible to draw definitive conclusions based on such a small patient population, particularly where median follow-up is only 17.7 months. Although there is a discrepancy between the plotted Kaplan-Meier and the reported OS outcomes, it can be observed that the timing of each OS event is hugely impactful in terms of summary statistics. This effect may have caused the difference in outcomes between Lam 2020 and CheckMate 142.

There are also minor differences in baseline characteristics, which may have had small impact on outcomes. Patients in Lam 2020 had a slightly worse ECOG score. This reflects the status of patients enrolled in an Individual Patient Supply Request Programme, who may have fewer treatment options and a poorer prognosis.

Indirect treatment comparison

A10. Priority question: Please provide more information on how the comparator studies for each of the matching-adjusted indirect comparisons (MAICs) were selected. Please provide the rationale for selecting a specific study for each comparison, and provide the specific rationale for excluding each of the other studies. Please also answer the following questions related to your choice of studies:

   a) **For NIVO+IPI, please provide the reference for and a description of Cohen et al. 2020 (Journal of Clinical Oncology 38(4), study name NIPICOL), how the results compare with Checkmate 142, and why this study was not presented in the company submission.**

NIPICOL is a French Phase II study undertaken by the GERCOR Multidisciplinary Oncology Cooperative Group. At the time of submission, limited information was available to inform this study. However, since submission, a manuscript has been accepted for publication.

NIPICOL study

The NIPICOL study is a Phase II, single-arm, open-label, multicentre study evaluating disease control rate (DCR) by RECIST and iRECIST in patients with dMMR/MSI mCRC treated with NIVO+IPI.[5, 6]

Eligible patients were ≥ 18 years old, had histologically confirmed mCRC locally assessed as MSI/dMMR, measurable disease per RECIST 1.1 criteria and had an ECOG performance score of 0 or 1. Patients were further required to have progressed on or after or were intolerant or contraindicated to current standard of

care, including: fluoropyrimidine, oxaliplatin and irinotecan; anti-EGFR therapy, if patients had wild-type RAS and RAF, and anti-VEGF therapy.[5, 6] In addition, patients were required to have an absolute neutrophil count ≥1500 cells per mm³, platelet count ≥100 x 10^9/L, haemoglobin ≥9 g/dL, serum creatinine level <150 µM, aspartate aminotransferase and alanine aminotransferase ≤3 × upper limit of normal (ULN; or ≤5 × ULN in the case of known liver metastases), alkaline phosphatase <5 × ULN, and total bilirubin ≤1.5 × ULN.[5, 6]

After the induction period, consisting of nivolumab 3 mg/kg intravenously over 60 min and ipilimumab 1 mg/kg intravenously over 90 min every 3 weeks for four cycles, patients continued to receive 3 mg/kg intravenously every 2 weeks until PD, discontinuation because of toxicity, death, withdrawal of consent, or for a maximum of 20 infusions (max. 1 year of therapy).[5, 6]

Primary outcome of this study was disease control rate (defined as the number of patients with stable disease (SD), partial response (PR), or complete response (CR) divided by the total number of patients) at 12 weeks according to RECIST 1.1 and iRECIST criteria by central review. Secondary outcomes included: PFS (defined as time from data of first dose of study treatment to date of first progression [RECIST 1.1 or iRECIST] or death due to any cause, up to 24 months); objective response rate (according to RECIST and iRECIST);OS (defined as the time between date of the first dose of study treatment and death); and safety outcomes.[5, 6]

Response rates at 12 weeks and overall best observed response is presented in Table 5. At 12 weeks, disease control rate was 86% by RECIST 1.1 and 87.7% by iRECIST (96%CI, 0.77-1.0 with no significant difference). At 12 months, PFS and OS per RECIST 1.1 were 72.9% (95% CI 59.0% - 82.7%) and 84.0% (95% CI 71.4% -91.3%), respectively. Median survivals were not reached.[5]

Table 5. NIPICOL[5]: Tumour response at 12 weeks and overall best observed response per RECIST 1.1 criteria

	At 12 weeks N=57	Overall best response N=57
Complete response, n (%)	2 (3.5)	11(19.3)
Partial response, n (%)	18 (31.6)	23 (40.4)
Objective response rate, %	35.1	59.6
Stable disease, n(%)	29 (50.9)	17(29.8)
Progressive disease, n (%)	5 (8.8)	3 (5.3)
Confirmed progressive disease per iRECIST criteria	4 (7.0)	2 (3.5)
Pseudo-progression per iRECIST criteria	1 (1.8)	1 (1.8)
Non-evaluable, n(%)	3 (5.3)	3 (5.3)
Disease control rate per RECISTS 1.1/ iRECIST, %	86.0/ 87.7	89.5/91.2
RECIST: Response Evaluation Criteria in Solid Tumours		

Comparison between NIPICOL and CheckMate 142

Based on a median follow-up time of 18.4 months, median PFS and OS have not been reached in the NIPICOL study.[5] However, outcomes at 12 months were broadly comparable to CheckMate 142. PFS was 72.9% in the NIPICOL study versus ▮ in the CheckMate 142 (investigator-assessed outcomes). OS was 84.0% in the NIPICOL study versus 84.9% in CheckMate 142. While the objective response rate (ORR) was comparable between the two studies (59.6% for NIPICOL study versus ▮ for CheckMate 142), more patients in the NIPICOL study achieved complete response (19.3% versus ▮).[5, 7]

It should be noted that these outcomes can be considered broadly comparable, despite shorter duration of treatment during NIPICOL, where patients received nivolumab 3 mg/kg intravenously over 60 min and ipilimumab 1 mg/kg intravenously over 90 min every 3 weeks for four cycles (induction phase) and then nivolumab 3 mg/kg intravenously every 2 weeks until progressed disease, discontinuation because of toxicity, death, withdrawal of consent, or for a maximum of 20 infusions, equivalent to 1 year of therapy.[5, 7] This supports the clinical relevance of the two-year stopping rule applied in CheckMate 8HW, and recently implemented in CheckMate 142. Further, this supports the long-term clinical outcomes in patients where a stopping rule is applied.

b) **For folinic acid, fluorouracil and irinotecan (FOLFIRI), please provide the rationale for using Van Cutsem 2012 in the economic model, although Tabernero 2015 was considered of equivalent relevance.**

Both studies were considered relevant to the decision problem, as both were large studies enrolling patients with similar patient characteristics to CheckMate 142. Van Cutsem 2012[8] (VELOUR) was considered to be more reflective of UK clinical practice and therefore was chosen over Tabernero 2015[9] (RAISE). However, a scenario analysis using Tabernero 2015[9] (RAISE) was presented Section B.3.8.3.4 of the company submission, showing similar ICERS.

A11. Priority question: Please re-assess which studies to include in the MAICs for the comparisons with folinic acid, fluorouracil and oxaliplatin (FOLFOX), FOLFIRI, trifluridine-tipiracil, and best supportive care (BSC). Please prioritise availability of Kaplan–Meier (KM) survival data but place greater weight on studies reporting patient characteristics for important prognostic factors such as BRAF/KRAS status. If limiting the selection by study size or to a specific subgroup, please specify and justify the sample size used as a cut off and the rationale for focusing on the subgroup.

a) **If there are a number of potentially relevant studies based on the criteria listed above, please prioritise randomised controlled trials (RCTs) over observational or non-comparative studies. The ERG suggests not to limit the selection to studies informing NICE submissions or marketing authorisations.**

b) **If there is no clear rationale for using one study over others available for a specific comparator, please use the study with the best outcomes for the comparator as this will provide a conservative estimate of the relative treatment effect versus NIVO+ IPI.**

Analysis of KRAS/BRAF mutation status

There is poor reporting of KRAS/BRAF for relevant comparators. This is typically undertaken in more recent studies and in studies enrolling more heavily treatment-experienced patients, due to the recent evolution in knowledge around these prognostic factors. Further, there is a large degree of difference in how this status is assessed and reported between comparator studies (i.e., KRAS versus RAS, analyses specifically assessing mutations in exon 2 of the KRAS gene versus analyses assessing the entirety of the gene, methodology for assessing mutations). Additionally, where this assessment is undertaken, it is most commonly reported in studies where it informs eligibility criteria (i.e., included patients must have be KRAS wildtype or mutation). These factors limit the extent to which informative analyses can be undertaken.

Further, adjusting to comparator KRAS/BRAF status is of limited relevance to the MSI-H/dMMR population. There is a higher incidence of KRAS/BRAF mutation in MSI-H/dMMR patients than the overall mCRC population, reflected in the proportion of patients with these mutations within the CheckMate 142 cohort. Based upon the subgroup analyses performed in CheckMate 142, presence or absence of these mutations may have less of an impact upon outcomes than has been observed in the general population, and therefore it has not been necessary to adjust for imbalances when comparing CheckMate 142 to external data in external populations: the outcomes do not greatly vary dependent upon the proportion with mutations (■Figure 6). Conversely, one may be concerned with the outcome of patient populations receiving comparator therapies given the incidence of mutation seen in MSI-H/dMMR patients, which are associated with worse prognosis. The modification of the evaluated treatment effect between the adjusted CheckMate 142 data and the comparator due to the invariance of outcomes in the NIVO+IPI receiving population versus the worsening outcomes expected in the modelled comparator receiving population, is

not expressed by applying a conditional constant treatment effect, with the expected direction of bias favouring the comparator. Without patient-level data from the comparator study or an external validated complete conditional outcomes model for the comparator, this cannot be compensated for. Given that the direction of bias is believed to favour the comparator both by consideration of this observed confounding and the expected unobserved confounding by the MSI-H/dMMR subpopulation, this is left unresolved.

Despite these factors, scenario analyses are provided where these factors are taken into account. For the purposes of these analyses, it is assumed that KRAS exon 2 wildtype is equivalent to wildtype in all other exons. Further, it is assumed that methodology for assessing mutations are equivalent. One final assumption is that eligibility criteria is followed, so that all patients in a study enrolling KRAS wildtype patients are KRAS wildtype (and vice versa), unless specifically reported otherwise.

Figure 6: CheckMate 142 N+I KRAS/BRAF subgroup analysis.
(a) – Overall survival
(b) – Progression-free survival per investigator

Study selection

All RCTs with available OS Kaplan-Meier are presented in Table 6 to Table 11. Each study was assessed for suitability for inclusion into the MAIC, with particular reference to the UK MSI-H/dMMR mCRC patient population, data availability and comparability to the CheckMate 142 baseline characteristics. Decisions and rationale are presented within the tables.

Base case analyses remained as per the company submission; however, these were updated to reflect available KRAS data (where available) and in line with other clarifications on the MAIC. Scenario analyses are provided versus alternative data sources, in line with the stated prioritisation from the ERG (BRAF/KRAS status; most improved outcomes favouring the comparator). The rationale and key eligibility criteria for inclusion or exclusion is also reflected.

Table 6 Study selection: FOLFOX

Study	CONFIRM 2[10]	NO16967[11]	ECOG E3200[12]	N9841[13]	NCT01111604[14]	CAPRI-GOIM[15]	TRICC-C[16]
Year	2011	2008	2007	2009	2016	2016	2019
Study ID in clinical SLR extraction grid	#247	#701_2	#1833	#1454_2	#1035	#2162	#10231
Additional IDs	-	-	#6139	-	-	-	-
Decision	**Base case analysis**	**Scenario**	Not used	Not used	Not used	**Scenario***	Not used
Key reason for decision (Base case, scenario, or not used)	Large scale RCT; relevant patient pathway; patient characteristics similar to CM142	Large scale RCT; relevant patient pathway; patient characteristics similar to CM142	Poorer patient outcomes	Patient pathway not relevant (excludes irinotecan/oxaliplatin-based regimens in first-line and mandates irinotecan monotherapy in third-line setting)	Regimen similar to UK practice, KRAS status known; small sample size; no age data available; outcomes comparable to other studies	Restricted patient population to following Cetuximab+FOLFIRI; Italy-specific; however most optimistic outcomes for comparators	Small sample size; poorer outcomes
Intervention	FOLFOX-4 + Placebo	FOLFOX-4	FOLFOX-4	FOLFOX-4	mFOLFOX-6	FOLFOX-4	FOLFOX
N (ITT)	429	314	291	246	49	79	26
Treatment experience	1 prior therapy (irinotecan. + fluoropyrimidine)	1 prior therapy (irinotecan + 5-fluorouracil/folinic acid +- biologic)	1 prior therapy (irinotecan + fluoropyrimidine required; prior oxaliplatin/bevacizumab was excluded)	1 prior therapy (fluoropyrimidine; prior irinotecan/oxaliplatin was excluded)	1 prior therapy (FOLFIRI / CAPIRI; prior biologic was allowed)	1 prior therapy (cetuximab plus FOLFIRI)	Refractory to non-oxaliplatin-based palliative first-line therapy
Life expectancy	≥12 weeks	>3 months	No criterion reported	>12 weeks	≥6 months	No criterion reported	No criterion reported
ECOG	WHO PS 0-2	ECOG 0-2	ECOG 0-2	ECOG 0-2	ECOG 0-1		
KRAS mutation (% observed cases)	NR	NR	NR	NR	61	27.4%	NR
BRAF mutation (% observed cases)	NR	NR	NR	NR	NR	6.0%	NR
OS median (months)	11.9	12.6	10.8	13.8	12.34	14	9.9
PFS median (months)	4.2	4.8	4.7	6.2	4.23	4.5	4.6

CAPIRI: irinotecan and capecitabine, ECOG: Eastern Cooperative Oncology Group; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan; FOLFOX: 5 fluorouracil, folinic acid, and oxaliplatin
* Scenario assessed as it represents most optimistic outcomes for the comparator

Table 7 Study selection: FOLFIRI

Study	RAISE[9]	VELOUR[8]	20070307[17] (NCT00752570)	LCCC1029[18] (NCT01298570)	NCT00967616[19]	Graeven et al[20]	FIRIS[21]
Year	2015	2016	2013	2018	2014	2007	2010
Study ID in clinical SLR extraction grid	#363	#240	#840	#641_1	#5220	#1767_1	#1005
Additional IDs	-	#240A	-	#2731, #9903	-	-	#4996
Decision	**Scenario**	**Base case analysis**	Not used	Not used	Not used	Not used	Not used
Key reason	Large study, representative median outcomes, treatment history required bevacizumab plus FOLFOX, which is not relevant to UK treatment pathway	Large study, representative median outcomes, treatment history similar to CM142	Small sample size; poorer outcomes	Small sample size	Small patient numbers; limited data; only published as poster	Small sample size; poorer outcomes	Japanese only study; 78.9% of patients received subsequent treatment
Intervention	FOLFIRI	FOLFIRI	FOLFIRI	FOLFIRI	FOLFIRI	FOLFIRI	FOLFIRI
N (ITT)	536	550	49	61	50	28	213
Treatment experience	1 prior therapy (bevacizumab + oxaliplatin + fluoropyrimidine)	1 prior therapy (oxaliplatin-containing therapy)	1 prior therapy (fluoropyrimidine + oxaliplatin therapy)	1 prior therapy (oxaliplatin + fluoropyrimidine /capecitabine +- biologic; prior irinotecan therapy was excluded)	1 prior therapy (prior irinotecan therapy was excluded)	1 prior therapy (5-fluorouracil /folinic acid, capecitabine or 5-fluorouracil /folinic acid in combination with oxaliplatin; prior irinotecan therapy was excluded)	1 prior therapy (prior irinotecan therapy was excluded)
Life expectancy	No criterion reported	No criterion reported	≥3 months	No criterion reported	No criterion reported	≥3 months	No criterion reported
PS	ECOG 0-1	ECOG 0-2	ECOG 0-1	ECOG 0-1	ECOG 0-2	ECOG 0-2	ECOG 0-1
KRAS mutation (% observed cases)	48.7	NR	32.6	67.3	NR	NR	NR
BRAF mutation (% observed cases)	NR	NR	NR	NR	NR	NR	NR
OS median	11.7	12.06	8.8	11.7	12.2	9.5	17.4
PFS median	4.5	4.67	5.2	5.3	4.2	3.7	5.1
ECOG: Eastern Cooperative Oncology Group; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan; OS: overall survival; PFS: progression-free survival							

Table 8 Study selection: FOLFIRI (continued)

Study	Xie[22]	NCT01479465[23]	Cao[24]	CAPTEM (NCT02414009)[25]
Year	2014	2017	2014	2020
Study ID in clinical SLR extraction grid	#110	#1689	#2291	#805_1
Additional IDs	-	-	-	-
Decision	Not used	**Scenario***	Not used	Not used
Key reason	Single-centre, Chinese study; low outcomes	Small patient numbers; US patients only; KRAS mutant only; best comparator outcomes; excluding FIRIS study	Chinese study; small patient population; poorer outcomes than other studies	Italian study; poorer outcomes; small sample size
Intervention	FOLFIRI	FOLFIRI	FOLFIRI	FOLFIRI
N (ITT)	155	80	77	43
Treatment experience	Prior oxaliplatin plus 5-fluorouracil-based first-line chemotherapy	Prior oxaliplatin plus 5-fluorouracil -based first-line chemotherapy	Prior first-line oxaliplatin-containing regimen	Prior oxaliplatin-based regimens, with or without bevacizumab
Life expectancy	No criterion reported	> 3 months	No criterion reported	No criterion reported
PS	ECOG 0-2	ECOG 0-2	ECOG 0-2	ECOG 0-1
KRAS mutation (% observed cases)	NR	100	NR	100
BRAF mutation (% observed cases)	NR	NR	NR	NR
OS median	10.7	16.3	11.3	10.6
PFS median	4.2	5.8	5.1	3.5
ECOG: Eastern Cooperative Oncology Group; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan; OS: overall survival; PFS: progression-free survival				
* Scenario assessed as it represents most optimistic outcomes for the comparator				

Table 9 Study selection: Trifluridine-tipiracil

Study	EudraCT, 2016–005241–23[26]	RECOURSE[27]	TERRA[28]	J003-10040030[29]
Year	2020	2015	2018	2012
Study ID in clinical SLR extraction grid	#815	#1123_1	#106	#40
Additional IDs	#3140, #10054	#4386	-	#4212, #5885, #6193
Decision	Not used	**Base case analysis**	**Scenario***	Not used
Key reason	Small sample size; Danish study	NA	30 study sites in China, the Republic of Korea and Thailand	Japanese study
Intervention	Trifluridine–tipiracil	Trifluridine–tipiracil	Trifluridine–tipiracil	Trifluridine–tipiracil
N (ITT)	47	534	271	112
Treatment experience	Refractory or intolerant to irinotecan and oxaliplatin (+ other criteria)	≥2 prior therapies (possibly including adjuvant if recur within 4 months)	Refractory or intolerant to two or more prior chemotherapy regimens (fluoropyrimidine, irinotecan, and oxaliplatin)	Previous treatment history of two or more regimens of standard chemotherapy; and were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin
Life expectancy	≥3 months	No criterion reported	No criterion reported	No criterion reported
ECOG	WHO 0-1	ECOG 0-1	ECOG 0-1	ECOG 0-2
KRAS mutation (% observed cases)	61.7	50.9	36.5	45.5
BRAF mutation (% observed cases)	0	NR	NR	NR
OS median	6.7	7.2	7.8	9
PFS median	2.6	2	2	2.7
ECOG: Eastern Cooperative Oncology Group; OS: overall survival; PFS: progression-free survival * Scenario assessed as it represents most optimistic outcomes for the comparator				

Table 10 Study selection: Best supportive care

Study	LUME-colon 1[30] (NCT02149108)	RECOURSE[27]	CO.23 (NCT01830621)[31]	Rao[32]	CO.26[33]	NCT01507545[34]	NCT02196688[35]	TERRA[28]
Year	2016	2015	2018	2004	2019	2018	2017	2018
ID	#225	#1123_2	#1524	#750	#2224_1	#1747	#101	#106
Additional	#7836, #3995	#4386_2	-	-	-	-	-	-
Decision	**Scenario**	**Base case analysis**	Not used	Not used	Not used	Not used	Not used	**Scenario**
Key reason	Large study; patients are more treatment experienced	Large study; reflects CM142 and comparator studies	Patients are more treatment experienced; poorer outcomes	UK study, but patients are older	Small sample size; poorer outcomes	Small sample size	Small sample size; poorer outcomes	Japanese
Intervention	Best supportive care + Placebo	Best supportive care + Placebo	Best supportive care + Placebo	Best supportive care	Best supportive care	Best supportive care + Placebo	Best supportive care	BSC
N (ITT)	382	266	144	133	61	42	24	135
Treatment experience	All available standard therapies (5-fluorouracil, oxaliplatin, irinotecan, bevacizumab/aflibercept, cetuximab/panitumumab (for RAS wild-type)	≥2 prior therapies (possibly including adjuvant therapy if recurrence occurred within 4 months)	All available standard therapies (fluoropyrimidine, oxaliplatin, irinotecan failed or contraindicated; EGFR inhibitor failed for RAS wild type unless unsuitable; VEGF was permitted but not required)	≥2 prior therapies based upon site	All available standard therapies (fluoropyrimidine, irinotecan, oxaliplatin, cetuximab or panitumumab failed for RAS wild type unless unsuitable; VEGF permitted but not required)	All available standard therapies (fluoropyrimidine, irinotecan, oxaliplatin, bevacizumab. EGFR inhibitors failed for RAS wild type)	Patients had to have received at least a second-line standard therapy, including fluoropyrimidine, oxaliplatin, or irinotecan-based regimens	Refractory or intolerant to two or more prior chemotherapy regimens (fluoropyrimidine, irinotecan, and oxaliplatin)
Life expectancy	≥12 weeks	No criterion reported	No criterion reported	No criterion reported	≥12 weeks	≥3 months	≥12 weeks	No criterion reported
ECOG PS	ECOG 0-1	ECOG 0-1	ECOG 0-1	ECOG 0-2	ECOG 0-1	ECOG 0-1	ECOG 0-1	ECOG 0-1
KRAS mutation (% observed cases)	53.9	50.8	47.2	37.8	60	46.3	NR	37.0%
BRAF mutation (% observed cases)	NR	NR	NR	NR	14	7.692307692	NR	NR
OS median	6	5.2	4.8	6.2	4.1	6.14	5.52	7.1
PFS median	1.4	1.7	1.8	2.6	1.9	1.86	0.99	1.8

ECOG: Eastern Cooperative Oncology Group; OS: overall survival; PFS: progression-free survival

Table 11 Study selection: BSC (continued)

Study	FRESCO[36]	CONCUR[37]	CORRECT[38]	Cunningham[39]	MCBRVP (NCT01413295)[40]	20020408 (NCT00113763)[41]	Barni[42]	J003-10040030[29]	20100007 (NCT01412957)[43]
Year	2018	2015	2013	1998	2016	2007	1995	2012	2016
ID	#1294	#1295	#1746	#2088_2	#2309	#234	#2440	#40_2	#4390
Additional	-	-	-	#2091_1	-			#4212, #5885, #6156, #6193	#1426_2
Decision	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used
Key reason	China study	Asian study	More treatment experienced; poorer outcomes	Small sample size; limited data	Small sample size; Spanish study; poorer outcomes	Limited data	Small sample size; limited data; patient pathway not reflective of current treatment pathway in the UK	Japanese study; small sample size	KRAS wild type patients
Intervention	Best supportive care	Best supportive care	Best supportive care	Best supportive care	Best supportive care	Best supportive care	Best supportive care	Best supportive care	Best supportive care
N (ITT)	138	68	255	90	24	232	25	57	188
Treatment experience	Metastatic CRC that progressed following at least 2 standard chemotherapy regimens	≥ 2 prior therapies (including fluoropyrimidine + oxaliplatin or irinotecan; prior bevacizumab, cetuximab, or panitumumab was allowed but not required)	Patients had to have received locally and currently approved standard therapies Includes as many of the following as were licensed: a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab; and cetuximab or panitumumab	Prior 5-fluorouracil regimen; no more than two prior palliative 5-fluorouracil, regimens	≥ 2 prior therapies	Two or three prior regimens for metastatic CRC	Patients who did not respond to a first-line chemotherapy with 5-fluorouracil, plus folates, or progressed after initial response or disease stabilisation	Previous treatment history of two or more regimens of standard chemotherapy; and were refractory or intolerant to a fluoropyrimidine, irinotecan, and oxaliplatin	Previously received a thymidylate synthase inhibitor (e.g. fluoropyrimidine, capecitabine, raltitrexed or fluorouracil-uracil)

	≥12 weeks	≥3 months	for patients who had KRAS wild-type tumours ≥3 months	No criterion reported	No criterion reported	No criterion reported	No criterion reported	No criterion reported	No criterion reported
Life expectancy	≥12 weeks	≥3 months	≥3 months	No criterion reported	No criterion reported	No criterion reported	No criterion reported	No criterion reported	No criterion reported
ECOG PS	ECOG 0-1	ECOG 0-1	ECOG 0-1	WHO 0-2	ECOG 0-2	ECOG 0-2	NR	ECOG 0-2	ECOG 0-2
KRAS mutation (% observed cases)	NR	38.3	61.6	NR	54.2	NR	NR	52	0
BRAF mutation (% observed cases)	NR	6.7	1.8	NR	NR	NR	NR	NR	NR
OS median	6.6	6.3	5	6.5	4.7	NR (approx. 7 months)	NR (approx. 9 months)	6.6	7.4
PFS median	1.8	1.7	1.7	NR	2.3	7.3 weeks	NR	1	1.7
ECOG: Eastern Cooperative Oncology Group; OS: overall survival; PFS: progression-free survival									

Baseline characteristics from selected studies

Baseline characteristics for eligible studies identified for FOLFOX are presented in Table 12 to Table 14, for FOLFIRI in Table 15 to Table 17, for trifluridine-tipiracil in Table 18 and Table 19, and BSC in Table 18 and Table 20.

Table 12. Baseline characteristics: CONFIRM 2[10] (FOLFOX base case analysis)

Characteristic		FOLFOX4 (n=429)	
		No.	%
Sex	Male	268	62.5
	Female	161	37.5
Race	White	356	83
	African American	16	3.7
	Asian	47	11
	Other	10	2.3
Age (years)	Mean	59.2	
	SD	11.31	
	Range	18-81	
Site of recurrence or metastasis	Liver	329	76.7
	Lung	188	43.8
	Lymph nodes, abdominal	50	11.7
	Lymph nodes, other	78	18.2
WHO PS	0	225	52.4
	1	182	42.4
	2	22	5.1
LDH	<1.5	303	70.6
	>1.5	126	29.4
Time since cancer diagnosis, months	Mean	23.43	
	SD	25.136	
	Median	14.03	
	Minimum	2.43	
	Maximum	200.7	
Number of prior lines of therapy	1	100%	
Highlighted rows indicate variables matched upon in base case. For this study, the "Primary" set was used.			

Table 13. Baseline characteristics: NO16967[11] (FOLFOX scenario analysis)

Characteristic		FOLFOX-4 (n=314)	
		No.	%
Gender	Male	191	61
	Female	123	39
Age, years	Median	59.7	
	Range	26–83	
ECOG performance status	0	145	46
	1	148	47
	2	21	7
Primary tumour site	Colorectal	24	8
	Colon	201	64
	Rectal	89	28
	Stage at first diagnosis		
	Local regional	129	41
	Metastatic	185	59
Prior treatment	Surgery	279	89
	Radiotherapy	70	22
Number of metastatic sites	1	108	34
	2	112	36
	3	60	19
	‡4	34	11
Alkaline phosphatase	Abnormal	145	46
	Normal	168	54
Number of prior lines of therapy	1	100%	

Highlighted rows indicate variables matched upon in base case. For this study, the "Secondary" set was used due to unacceptable patient weights on primary

Table 14. Baseline characteristics: CAPRI-GOIM[15] (FOLFOX scenario analysis)

		FOLFOX (n=79)	
		N	%
Gender	Male	43	54.4
	Female	36	45.6
Age	Median	63	
	Range	40-80	
Primary tumour site	Colon	52	65.9
	Rectum	27	34.1
Number of metastatic sites	1	47	59.5
	2	22	27.9
	3	10	12.6
Liver metastases only*		32	40.5
Prior adjuvant chemotherapy	Yes	13	16.5
	No	66	83.5

* As this was not specified as total proportion of patients with liver metastases, it was not included as a potential matching variable
Highlighted rows indicate variables matched upon in base case. For this study, the "Secondary" set was used due to unacceptable patient weights on primary, and identified no predictors among the available data other than age and sex

Table 15. Baseline characteristics: VELOUR[8] (FOLFIRI base case analysis)

Characteristic		FOLFIRI (n=614)	
		No.	%
ECOG PS	0	350	57
	1	250	40.7
	2	14	2.3
Prior bevacizumab	Yes	187	30.5
	No	427	69.5
Sex	Male	353	57.5
	Female	261	42.5
Age, years	Median	61	
	Range	19-86	
Primary site	Colon	302	49.2
	Rectosigmoid	136	22.1
	Rectum	174	28.3
	Other	2	0.3
No. of metastatic organs involved at baseline	0	6	1
	1	271	44.1
	>1	337	54.9
Metastatic organs involved at baseline	Any site	608	99
	Liver	431	70.2
	Lung	277	45.1
	Lymph nodes	181	29.5
	Peritoneum	88	14.3
Liver metastasis	None, or liver and other metastases	468	76.2
	Liver metastasis only	146	23.8
Prior hypertension		268	43.6
Prior chemotherapy	Adjuvant only	64	10.4
	Adjuvant and metastatic disease	108	17.6
	Metastatic disease	442	72

Highlighted rows indicate variables matched upon in base case. For this study, the "Secondary" set was used due to unacceptable patient weights on primary

Table 16. Baseline characteristics: RAISE[9] (FOLFIRI scenario analysis)

Characteristic		Placebo (n=536)	
Age (years)	Mean (range)	62 (33–87)	
	<65	321	60%
	≥65	215	40%
Sex	Male	326	61%
	Female	210	39%
Ethnic origin	White	410	77%
	Asian	103	19%

	Black	16	3%
	Other	2	<1%
	Not reported	5	1%
Geographical region	Europe	235	44%
	North America	143	27%
	Other	158	30%
ECOG	0	259	48%
	1	273	51%
	2 or 3	2	<1%
	Missing	2	<1%
Time to progression after start of first-line treatment	<6 months	129	24%
	≥6 months	407	76%
KRAS exon 2 status	Mutant	261	49%
	Wild type	275	51%
Carcinoembryonic antigen (µg/L)	<200	393	73%
	≥200	107	20%
	Missing	36	7%
Number of metastatic sites	1	157	29%
	2	194	36%
	≥3	182	34%
	Missing	3	1%
Site of primary tumour	Colon	358	67%
	Rectum	171	32%
	Colorectal	7	1%
Number of prior lines of therapy	1	100%	

Highlighted rows indicate variables matched upon in base case. For this study, the "Secondary" set was used due to unacceptable patient weights on primary

Table 17. Baseline characteristics: NCT01479465[23] (FOLFIRI scenario analysis)

Characteristic		FOLFIRI + Placebo (Part B)	
Overall Number of Baseline Participants		84	
Number Analysed		80	
Age	Mean (range)	58.8 (32, 85)	
	Between 18 and 65 years	57	71.3%
	≥ 65 years	23	28.7%
Sex	Female	41	51.2%
	Male	39	48.8%
Race	White	67	83.8%
	Black or African American	8	10.0%
	Asian	1	1.3%
	Native Hawaiian or Pacific Islander	1	1.3%
	Not Permitted	3	3.8%
	Missing	0	0.0%
Race/ ethnicity	Non-Hispanic/Latino	70	87.5%
	Hispanic/Latino	5	6.3%
	Not Permitted	5	6.3%

ECOG PS	0	43	53.8%
	1	36	45.0%
	2	1	1.3%
Metastatic sites	Liver	58	72.5%
	Lung	34	42.5%
	Lymph nodes	11	13.8%
KRAS wild type		0%	

Highlighted rows indicate variables matched upon in base case. For this study, the "Primary" set was used

Table 18. Baseline characteristics: RECOURSE[27] (trifluridine-tipiracil and BSC base case analysis)

Characteristic		TAS-102		Placebo	
		(n=534)		(n=266)	
Age	Median	63		63	
	Range	27–82		27–82	
Sex	Male	326	61	165	62
	Female	208	39	101	38
Race	White	306	57	155	58
	Asian	184	34	94	35
	Black	4	<1	5	2
Region*	Japan	178	33	88	33
	United States, Europe and Australia	356	67	178	67
ECOG	0	301	56	147	55
	1	233	44	119	45
Primary site of disease	Colon	338	63	161	61
	Rectum	196	37	105	39
KRAS mutations	No	262	49	131	49
	Yes	272	51	135	51
Time from diagnosis of metastases	<18 months	111	21	55	21
	≥18 months	423	79	211	79
Number of prior regimens	2	95	18	45	17
	3	119	22	54	20
	≥4	320	60	167	63
Prior systemic anticancer agents	Fluoropyrimidine	534	100	266	100
	Irinotecan	534	100	266	100
	Oxaliplatin	534	100	266	100
	Bevacizumab	534	100	265	>99
	Anti-EGFR monoclonal antibody	278	52	144	54
	Regorafenib	91	17	53	20
Refractory to fluoropyrimidine	As part of any prior treatment regimen	524	98	265	>99
	At time of last exposure	497	93	240	90
	As part of last regimen before study entry	311	58	144	54

Highlighted rows indicate variables matched upon in base case. For this study, the "Secondary" set was used due to unacceptable patient weights. Regional subgroup-specific aggregate data was used for this study.
*In this study, only the index-study overlapping North American/European subgroups were analysed, as Japanese patients were not represented in CheckMate 142. Within the two subgroups, proportion European was used as an adjustment factor (0/100% respectively)

Table 19. Baseline characteristics: TERRA[28] (trifluridine-tipiracil and BSC scenario analysis)

Characteristic		Trifluridine/ Tipiracil (n=271)		Placebo (n=135)	
Sex	Male	170	63	84	62
	Female	101	37	51	38
Age	Median (range)	58	(26-81)	56	(24-80)
	<65	206	76	103	76
	>= 65	65	24	32	24
Race	Asian	271	100	135	100
Country	China	204	75	101	75
	Republic of Korea	55	20	26	19
	Thailand	12	4	8	6
Height	Mean (SD), cm	165.4	7.6	165.7	7.6
Weight	Mean (SD), kg	64.4	11.8	63.6	11
BMI	Median (range), KM/M2	23.4	(15.8-36.1)	23	(12.9-31.6)
BSA	Median (range), m2	1.72	(1.29-2.20)	1.7	(1.26-2.02)
KRAS	Wild type	172	63	85	63
	Mutant	99	37	50	37
Median time since cancer diagnosis, months (range)		22.8	(2-166)	26.3	(1-102)
Primary tumour site	Colon	154	57	85	63
	Rectum	117	43	50	37
ECOG	0	64	24	30	22
	1	207	76	105	78
No of prior regimens	2	62	23	25	19
	3	74	27	36	27
	>=4	135	50	74	55
No of metastatic sites	1-2	166	61	82	61
	>=3	105	39	53	39
Time since first diagnosis of metastasis, months	Median (range)	18.6	(1.3-106.8)	23.3	(1.4-103.0)
	<18 months	134	49	52	39
	>= 18 months	137	51	83	61
Prior biologic	None	148	55	66	49
	Any (anti-VEGF or anti-EGFR or both)	123	45	69	51
	Anti-VEGF but not anti-EGFR	52	19	27	20
	Anti-EGFR but not anti-VEGF	46	17	25	19
	Both anti-VEGF and anti-EGFR	25	9	17	13

Highlighted rows indicate variables matched upon in base case. For this study, the "Secondary" set was used due to unacceptable patient weights on primary

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Table 20. Baseline characteristics: LUME Colon 1[28] (BSC scenario)

Characteristic		Placebo (n=382)	
Age	Median (range)	62	(23–83)
Sex	Male	218	57.1
Race	Caucasian	268	70.2
	Asian	104	27.2
	Other	3	0.8
	Missing	9	2.4
ECOG	0	142	37.2
	1	240	62.8
Region	Western Europe, North America, Australia	227	59.4
	Asia	98	25.7
	Other	57	14.9
Time from onset of metastatic disease until randomization (%)	<24 months	110	28.8
	>=24 months	272	71.2
Primary site of disease	Colon	227	59.4
	Rectum	154	40.3
	Unknown	1	0.3
>1 metastatic site at screening		319	83.5
Presence of liver metastases	Yes	266	69.6
	No	116	30.4
Previous treatments	Mean (SD) number of lines of previous systemic anticancer therapies	3.9	1.8
	>=3 lines of previous systemic anticancer therapies	296	77.5
Previous systemic anticancer therapies	Oxaliplatin	382	100
	Fluoropyrimidine	382	100
	Irinotecan	382	100
	Bevacizumab or aflibercept	381	99.7
	Bevacizumab	370	96.9
	Aflibercept	47	12.3
	Regorafenib	144	37.7
	Trifluridine/tipiracil	53	13.9
Previous radiotherapy		132	34.6
KRAS wild-type and other RAS wild-type patients only		176	46.10%
Prior cetuximab or panitumumab		175	99.4
Metastasis site	Liver	266	69.6%

Highlighted rows indicate variables matched upon in base case. For this study, the "Secondary" set was used due to unacceptable patient weights on primary

MAIC adjustment characteristics

To improve confidence in the results of the ITC, the potential set of adjustment characteristics was expanded from the company submission. In full, these characteristics were:

- **Age** – mean, standard deviation (sd), minimum, 25th percentile, median, 75th percentile, maximum. Where multiple was available, mean/sd were preferred. Among the selected studies, none reported at the 25th or 75th percentile.
- **Sex** – proportion male.
- **Race** – proportion Asian, proportion Black or African American. Due to the low absolute number of Asian patients in CheckMate 142, inclusion of this adjustment characteristic tended to concentrate on matching weights upon a very limited number of individuals, resulting in an infeasibly large change in outcomes from the unweighted reference case when adjusting to populations with higher proportion Asian. This was taken as an indication that the subgroup was not sufficiently sampled within CheckMate 142 for a reliable estimation of conditional outcome modification. This characteristic was therefore removed from consideration for the "secondary" set.
- **KRAS** – observed cases proportion wild-type. Patients in CheckMate 142 with unknown status were assigned the observed cases proportion.
- **BRAF** – observed cases proportion wild-type. Patients in CheckMate 142 with unknown status were assigned the observed cases proportion. In practice, only the CAPRI-GOIM provided a reliable measurement of BRAF mutation/wild-type among the selected studies, and was at a very low proportion.
- **ECOG PS** – proportion with ECOG PS 0.
- **Time from diagnosis** – mean, sd, minimum, median, maximum.
- **Tumour location** – proportion with primary location "rectum". Due to the low absolute number of patients with rectal tumours in CheckMate 142, inclusion of this adjustment characteristic tended to dramatically concentrate on matching weights upon a very limited number of individuals, resulting in an infeasibly large change in outcomes from the unweighted reference case, as with Asian race; the same action of exclusion from consideration within the "secondary" matching set was taken.
- **Number of prior therapies** – proportion with only a single prior therapy.
- **Region** – proportion of population attending study centres in Europe.
- **Metastases location** – proportion with liver metastases, proportion with lung metastases, proportion with peritoneal metastases, proportion with lymph node metastases.
- **Number of metastatic sites** – proportion with metastatic sites limited to a single organ.

In the updated analysis, four adjustment sets were assessed:

- **All** – All available prognostic factors. Full matching was not expected to be possible for all studies upon all factors given the limited study size of CheckMate 142, and so this was expected to be a scenario analysis for a limited set of comparisons only.
- **Primary: Predictive + demographic** – Variables predictive of outcomes from the patient-level data within CheckMate 142 plus age and sex. To identify this predictive subset of variables from the study specific "All" set, forward stepwise selection was performed within a Cox proportional hazards

model upon the CheckMate 142 data. The criterion for inclusion of a predictive variable was improvement in 10-fold cross validated partial likelihood. Age and sex were deemed necessary for inclusion in extrapolation given the lifetable component of the survival models of NIVO+IPI, irrespective of their prognostic relevance in the within-trial period to which the Cox models were fitted.

- **Secondary**: as per the primary adjustment set, but removal of the following: proportion of patients specified as Asian; proportion of patients where primary tumour location is specified as rectum.
- **Fallback: Demographic** – Age and sex alone, providing a fallback model in case of overly-concentrated patient weights.

MAIC results

Outcomes for the MAIC are provided in Table 22 (Overall survival) and Table 23 (Progression-free survival), with adjustment of CheckMate 142 Kaplan-Meier depicted in Figure 7 to Figure 32. As can be observed, switching to alternative studies and inclusion of additional adjustment characteristics has minimal impact on outcomes, due to the long-term beneficial impact of NIVO+IPI. As an exception to this, adjustments where the effective study size was too low provided spurious results, including the comparison versus FOLFIRI from NCT01479465, where FOLFIRI mean OS was adjusted from 20.97 months to 41.4 months.

A summary of comparator survival outcomes from MAIC analyses is provided in Table 21.

Table 21. Summary of comparator outcomes from MAIC analyses

	Mean OS (CM 142 population modelled as receiving comparator)	Mean PFS (CM 142 population modelled as receiving comparator)
FOLFIRI	17.2–41.4 months	4.5–10.3 months
FOLFOX	13.5–21.8 months	5.9–7.0 months
Trifluridine-tipiracil	8.5–15.7 months	3.4–4.3 months
BSC	6.2–10.8 months	1.6–2.1 months
BSC: best supportive care: FOLFIRI: 5 fluorouracil, folinic acid and irinotecan; FOLFOX: 5 fluorouracil, folinic acid, and oxaliplatin; OS: overall survival; PFS: progression free survival		

Table 22. MAIC output: Overall survival outcomes

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)		ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	Original
CheckMate 142	NIVO+IPI	119	168.13	5.12 (0.177)							
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	200.5	5.30 (0.200)	2.45 (0.205)	14.52	15.65
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	173.9	5.16 (0.193)	2.52 (0.198)	13.50	NA
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	163.3	5.10 (0.211)	2.04 (0.241)	21.80	NA
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	144.6	4.97 (0.210)	2.19 (0.220)	18.87	17.19
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	120.4	4.79 (0.178)	2.04 (0.184)	21. 92	15.30
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	85.2	4.44 (0.368)	1.40 (0.403)	41.40	NA
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	113.4	4.73 (0.234)	2.39 (0.249)	15.41	10.86
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	163.4	5.10 (0.192)	2.64 (0.300)	12.05	11.70
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	229.9	5.44 (0.131)	2.99 (0.146)	8.48	NA
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	112.8	4.73 (0.231)	2.75 (0.305)	10.77	7.55
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	185.6	5.22 (0.194)	3.14 (0.521)	7.31	8.13
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	181.8	5.20 (0.178)	2.88 (0.220)	9.47	NA
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	235.5	5.46 (0.114)	3.30 (0.135)	6.21	NA
ESS: effective sample size; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan; FOLFOX: 5 fluorouracil, folinic acid, and oxaliplatin; se: standard error											

Table 23. MAIC output: Progression-free survival outcomes

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)		ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	Original
CheckMate 142	NIVO+IPI	119	69.8	4.25 (0.185)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	64.4	4.16 (0.226)	2.46 (0.229)	5.94	7.54
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	68.6	4.23 (0.220)	2.55 (0.224)	5.45	NA
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	66.8	4.20 (0.217)	2.30 (0.246)	7.00	NA
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	58.8	4.07 (0.189)	2.18 (0.194)	7.86	6.33
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	49.1	3.89 (0.202)	1.98 (0.207)	9.66	4.49
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	55.2	4.01 (0.512)	1.91 (0.526)	10.34	NA
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	59.9	4.09 (0.189)	2.79 (0.220)	4.29	4.19
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	74.9	4.32 (0.189)	3.03 (0.270)	3.38	3.70
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	83.2	4.42 (0.187)	3.04 (0.739)	3.35	NA
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	59.5	4.09 (0.190)	3.48 (0.193)	2.14	2.10
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	78.3	4.36 (0.189)	3.73 (0.211)	1.67	1.90
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	62.1	4.13 (0.241)	3.50 (0.330)	2.12	NA
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	87.2	4.47 (0.222)	3.79 (0.225)	1.58	NA
ESS: effective sample size; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan; FOLFOX: 5 fluorouracil, folinic acid, and oxaliplatin; se: standard error											

FOLFOX comparisons

Table 24: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: CAPRI-GOIM

Variable	CAPRI-GOIM (FOLFOX) Unadjusted Value	CheckMate 142 Nivolumab + Ipilimumab Unadjusted Value	Matched (Secondary set) Matched?	Matched (Secondary set) Value
N/ESS	79	119		98.6
Age (years) - min	40	21	Y	40
Age (years) - median	63	58	Y	62.4
Age (years) - max	80	88	Y	80
Sex - Male - %	54.40%	58.80%	Y	54.40%
KRAS - wild type - %	100.00%	58.10%		58.80%
Primary tumour location - rectum - %	34.20%	5.00%		4.80%
Met. Locations - 1 - %	59.50%	25.20%		24.40%
ESS: effective sample size; FOLFOX: 5 fluorouracil, folinic acid, and oxaliplatin				
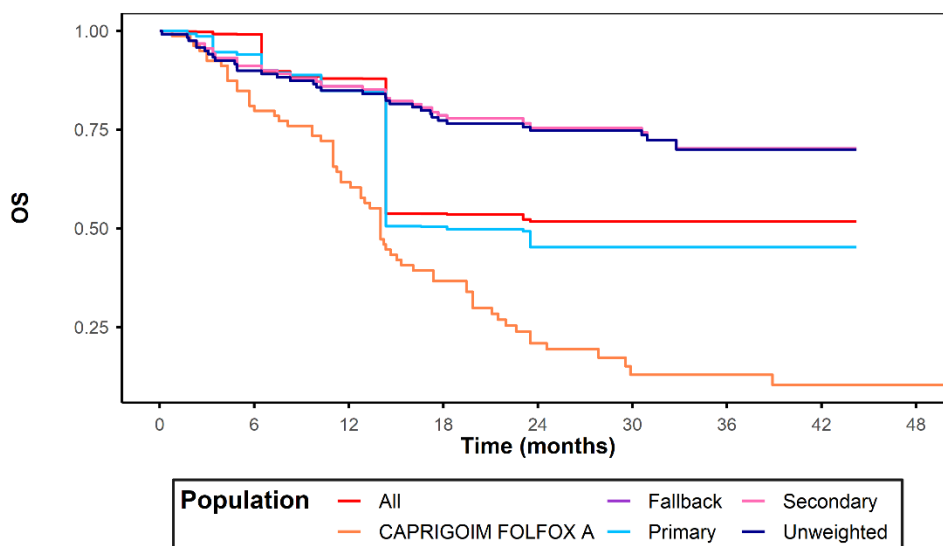
NAR (Cumulative Events)

All	6.4 (0.0)	6.4 (0.1)	5.7 (0.8)	3.5 (3.0)	3.4 (3.1)	3.0 (3.1)	0.2 (3.1)	0.1 (3.1)	0.0 (3.1)
Fallback	98.6 (0.0)	90.7 (8.7)	85.9 (13.9)	78.3 (21.1)	75.5 (24.3)	60.3 (24.3)	15.3 (27.0)	12.5 (27.0)	0.0 (27.0)
Primary	7.4 (0.0)	7.0 (0.4)	6.6 (1.1)	3.8 (3.7)	3.7 (4.1)	2.8 (4.1)	0.5 (4.1)	0.4 (4.1)	0.0 (4.1)
Secondary	98.6 (0.0)	90.7 (8.7)	85.9 (13.9)	78.3 (21.1)	75.5 (24.3)	60.3 (24.3)	15.3 (27.0)	12.5 (27.0)	0.0 (27.0)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 7. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: CAPRI-GOIM Overall survival
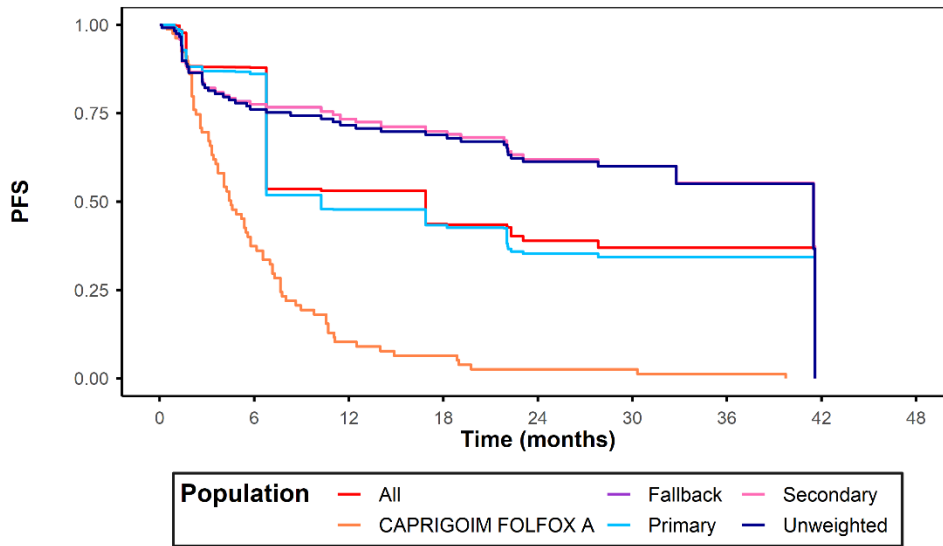
NAR (Cumulative Events)

All	6.4 (0.0)	5.6 (0.8)	3.4 (3.0)	3.4 (3.6)	2.5 (3.9)	1.4 (4.0)	0.1 (4.0)	0.0 (4.0)	0.0 (4.0)
Fallback	98.6 (0.0)	75.1 (21.9)	69.5 (25.9)	64.1 (29.0)	55.4 (36.1)	30.1 (37.3)	9.2 (38.1)	0.0 (40.5)	0.0 (40.5)
Primary	7.4 (0.0)	6.4 (1.0)	3.6 (3.9)	3.2 (4.2)	2.4 (4.7)	1.3 (4.8)	0.4 (4.8)	0.0 (4.8)	0.0 (4.8)
Secondary	98.6 (0.0)	75.1 (21.9)	69.5 (25.9)	64.1 (29.0)	55.4 (36.1)	30.1 (37.3)	9.2 (38.1)	0.0 (40.5)	0.0 (40.5)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 8. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: CAPRI-GOIM progression-free survival

Table 25: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: CONFIRM2

Variable	CONFIRM2 (FOLFOX)	CheckMate 142 Nivolumab + Ipilimumab		
	Unadjusted	Unadjusted	Matched (primary set)	
	Value	Value	Matched?	Value
N/ESS	429	119		21.4
Age (years) - mean	59.2	56.55	Y	59.2
Age (years) - sd	11.31	13.789	Y	11.31
Sex - Male - %	62.50%	58.80%	Y	62.50%
Race - Asian - %	11.00%	2.50%	Y	11.00%
Race - Black - %	3.70%	1.70%		5.00%
ECOG PS - 0 - %	52.40%	45.40%		49.40%
Time from diagnosis (years) - mean	1.95	2.57	Y	1.95
Time from diagnosis (years) - sd	2.095	2.823	Y	2.095
No. prior lines - 1 - %	100.00%	39.50%	Y	100.00%
Met. Loc. - Liver - %	76.70%	42.90%	Y	76.70%
Met. Loc. - Lung - %	47.80%	26.10%		31.20%
ECOG: Easter Cooperative Oncology Group; ESS: effective sample size; FOLFOX: 5 fluorouracil, folinic acid, and oxaliplatin; sd: standard deviation				
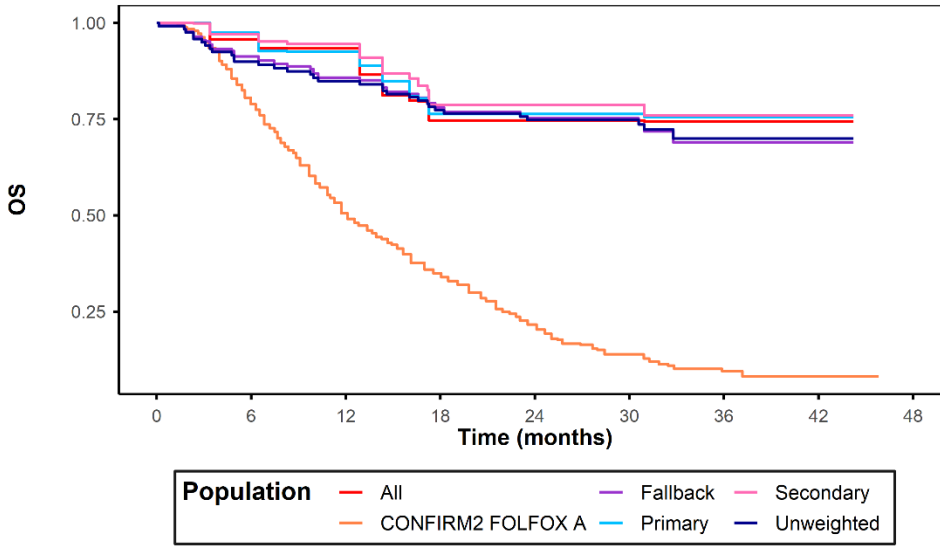
NAR (Cumulative Events)

All	18.6 (0.0)	18.6 (0.8)	17.4 (1.2)	14.8 (4.7)	14.8 (4.7)	11.7 (4.7)	2.7 (4.8)	2.6 (4.8)	0.0 (4.8)
Fallback	109.1 (0.0)	100.3 (9.5)	94.7 (15.5)	86.4 (23.9)	83.2 (27.0)	64.6 (27.0)	15.8 (30.6)	12.8 (30.6)	0.0 (30.6)
Primary	21.4 (0.0)	21.4 (0.5)	19.8 (1.6)	17.2 (5.1)	17.2 (5.1)	14.1 (5.1)	4.1 (5.2)	4.0 (5.2)	0.0 (5.2)
Secondary	31.9 (0.0)	31.8 (1.0)	30.3 (1.8)	26.3 (6.8)	26.3 (6.8)	20.1 (6.8)	6.0 (7.3)	5.5 (7.3)	0.0 (7.3)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 9. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: CONFIRM2 Overall survival
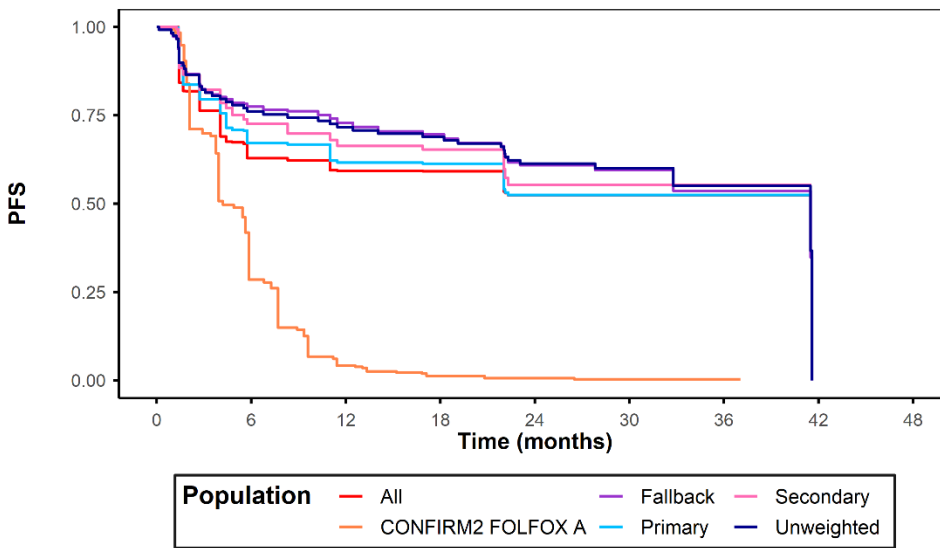
NAR (Cumulative Events)

All	18.6 (0.0)	11.7 (6.6)	10.4 (7.3)	10.3 (7.3)	9.2 (8.5)	4.6 (8.5)	1.2 (8.5)	0.0 (8.5)	0.0 (8.5)
Fallback	109.1 (0.0)	82.4 (24.3)	75.9 (29.1)	69.9 (32.3)	59.4 (40.9)	32.2 (41.9)	9.1 (43.0)	0.0 (45.3)	0.0 (45.3)
Primary	21.4 (0.0)	14.3 (6.7)	12.5 (7.8)	12.3 (7.9)	10.6 (9.6)	5.8 (9.6)	1.3 (9.6)	0.0 (9.6)	0.0 (9.6)
Secondary	31.9 (0.0)	22.3 (8.5)	20.1 (10.4)	19.6 (10.7)	16.9 (13.6)	6.7 (13.6)	4.4 (13.6)	0.0 (13.6)	0.0 (13.6)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 10. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: CONFIRM2 progression-free survival

Table 26: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: NO16967

| Variable | NO16967(FOLFOX) | CheckMate 142 Nivolumab + Ipilimumab | | |
| | Unadjusted | Unadjusted | Matched (secondary set) | |
	Value	Value	Matched?	Value
N/ESS	314	119		108.2
Age (years) - min	26	21	Y	26
Age (years) - median	59.7	58	Y	59.5
Age (years) - max	83	88	Y	81
Sex - Male - %	60.80%	58.80%	Y	60.80%
Race - Asian - %	14.00%	2.50%		2.10%
Race - Black - %	2.60%	1.70%		2.00%
ECOG PS - 0 - %	46.20%	45.40%	Y	46.20%
Primary tumour location - rectum - %	28.30%	5.00%		4.40%
No. prior lines - 1 - %	100.00%	39.50%		40.70%
Met. Locations - 1 - %	34.40%	25.20%	Y	34.40%
ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size; FOLFOX: 5 fluorouracil, folinic acid, and oxaliplati				

NAR (Cumulative Events)

All	12.8 (0.0)	12.8 (0.1)	12.2 (0.7)	11.4 (3.4)	11.4 (3.4)	8.8 (3.4)	1.6 (3.6)	1.2 (3.6)	0.0 (3.6)
Fallback	114.3 (0.0)	105.1 (10.1)	98.7 (16.8)	89.9 (25.3)	86.8 (28.6)	67.1 (28.6)	17.4 (31.7)	13.7 (31.7)	0.0 (31.7)
Primary	41.4 (0.0)	37.0 (6.3)	33.8 (7.9)	28.2 (13.5)	27.4 (14.3)	22.8 (14.3)	5.3 (16.5)	4.5 (16.5)	0.0 (16.5)
Secondary	108.2 (0.0)	100.7 (8.3)	93.6 (15.6)	85.6 (23.3)	82.5 (26.6)	64.1 (26.6)	16.6 (29.7)	12.6 (29.7)	0.0 (29.7)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 11. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: NO16967 Overall survival
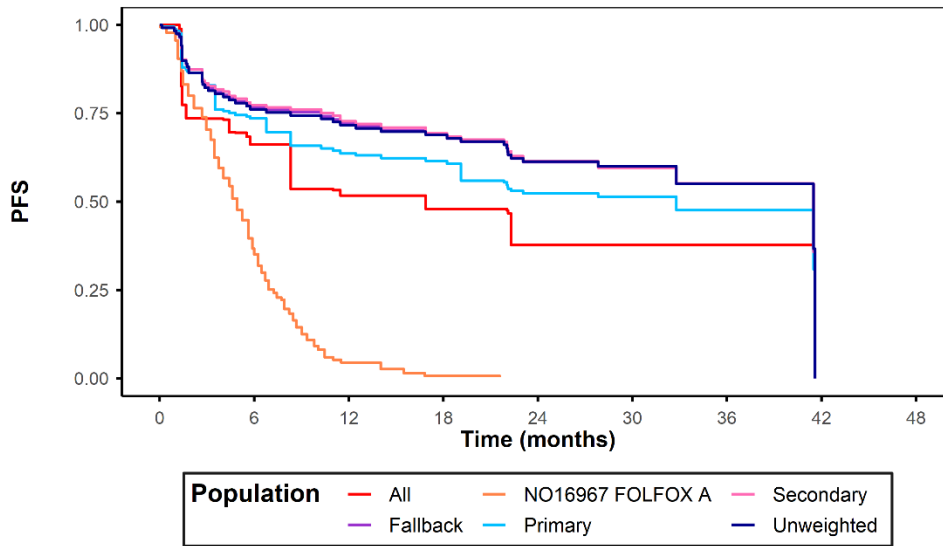
NAR (Cumulative Events)

All	12.8 (0.0)	8.4 (4.2)	6.5 (6.0)	6.3 (6.5)	5.7 (7.7)	3.5 (7.7)	1.2 (7.7)	0.0 (7.7)	0.0 (7.7)
Fallback	114.3 (0.0)	84.5 (26.2)	77.8 (31.2)	72.2 (34.4)	62.4 (42.4)	32.5 (43.4)	9.9 (44.3)	0.0 (46.5)	0.0 (46.5)
Primary	41.4 (0.0)	28.4 (10.6)	24.2 (14.4)	22.9 (15.2)	19.1 (18.6)	10.7 (18.8)	2.3 (19.0)	0.0 (19.5)	0.0 (19.5)
Secondary	108.2 (0.0)	80.1 (24.1)	74.6 (28.8)	69.4 (32.1)	60.1 (39.7)	31.0 (41.0)	8.9 (41.8)	0.0 (43.6)	0.0 (43.6)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 12. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: NO16967 progression-free survival

FOLFIRI comparisons

Table 27: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: NCT01479465

| Variable	NCT01479465 (FOLFIRI)	CheckMate 142 Nivolumab + Ipilimumab		
	Unadjusted	Unadjusted	Matched (primary set)	
	Value	Value	Matched?	Value
N/ESS	80	119		19.73
Age (years) - mean	58.8	56.55	Y	58.8
Age (years) - min	32	21	Y	33
Age (years) - max	85	88	Y	75
Sex - Male - %	48.80%	58.80%	Y	48.80%
Race - Asian - %	1.30%	2.50%	Y	1.30%
Race - Black - %	10.00%	1.70%		5.30%
KRAS – wild type - %	0.00%	58.10%	Y	10.70%
ECOG PS - 0 - %	53.80%	45.40%	Y	53.80%
Met. Loc. - Liver - %	72.50%	42.90%		63.60%
Met. Loc. - Lung - %	42.50%	26.10%	Y	42.50%
Met. Loc. - Lymph node - %	13.80%	62.20%	Y	13.80%
Met. Locations - 1 - %	17.50%	25.20%		18.00%
ESS: effective sample size; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan				
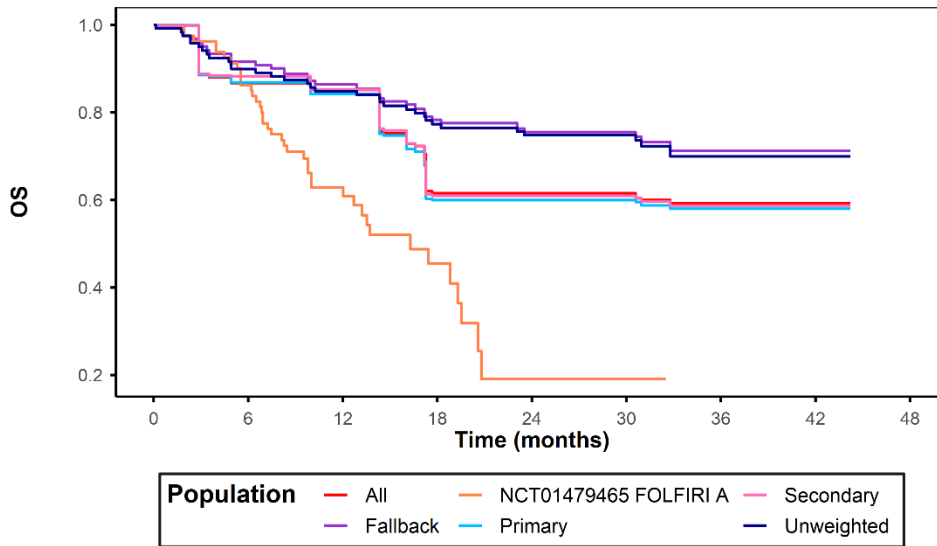
NAR (Cumulative Events)

All	18.2 (0.0)	16.0 (2.4)	15.8 (2.7)	11.3 (7.0)	11.3 (7.0)	9.6 (7.0)	4.3 (7.3)	4.2 (7.3)	0.0 (7.3)
Fallback	108.8 (0.0)	100.3 (9.2)	94.9 (14.8)	86.0 (23.6)	83.0 (26.6)	64.9 (26.6)	17.6 (29.0)	13.9 (29.0)	0.0 (29.0)
Primary	19.7 (0.0)	17.4 (2.6)	17.1 (3.1)	11.9 (7.9)	11.9 (7.9)	10.1 (7.9)	4.0 (8.1)	4.0 (8.1)	0.0 (8.1)
Secondary	20.2 (0.0)	17.9 (2.4)	17.8 (3.0)	12.4 (7.9)	12.4 (7.9)	10.5 (7.9)	4.1 (8.1)	4.1 (8.1)	0.0 (8.1)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 13. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: NCT01479465 Overall survival
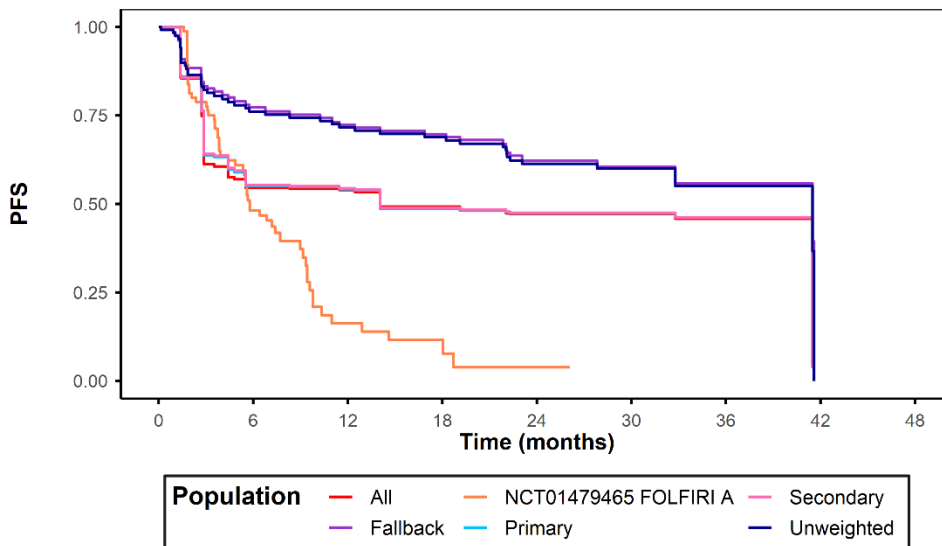
NAR (Cumulative Events)

All	18.2 (0.0)	8.2 (7.4)	7.7 (7.5)	7.4 (8.2)	6.1 (8.4)	4.5 (8.4)	1.8 (8.5)	0.0 (9.4)	0.0 (9.4)
Fallback	108.8 (0.0)	80.6 (24.3)	73.6 (29.3)	69.4 (31.9)	60.7 (39.2)	31.6 (40.4)	9.5 (41.2)	0.0 (43.3)	0.0 (43.3)
Primary	19.7 (0.0)	9.8 (8.2)	8.9 (8.4)	8.7 (9.3)	7.0 (9.5)	5.0 (9.5)	2.3 (9.5)	0.0 (10.4)	0.0 (10.4)
Secondary	20.2 (0.0)	10.2 (8.4)	9.3 (8.6)	9.0 (9.5)	7.3 (9.7)	5.1 (9.7)	2.3 (9.8)	0.0 (10.7)	0.0 (10.7)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 14. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: NCT01479465 progression-free survival

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Table 28: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: RAISE

| Variable | RAISE (FOLFIRI) | CheckMate 142 Nivolumab + Ipilimumab | | |
| | Unadjusted | Unadjusted | Matched (secondary set) | |
	Value	Value	Matched?	Value
N/ESS	536	119		91.1
Age (years) - mean	62	56.55	Y	62
Age (years) - min	33	21	Y	33
Age (years) - max	87	88	Y	81
Sex - Male - %	60.80%	58.80%	Y	60.80%
Race - Asian - %	19.20%	2.50%		1.70%
Race - Black - %	3.00%	1.70%		2.10%
KRAS – wild type - %	49.80%	58.10%	Y	49.80%
ECOG PS - 0 - %	48.30%	45.40%	Y	48.30%
Primary tumour location - rectum - %	31.90%	5.00%		6.30%
No. prior lines - 1 - %	100.00%	39.50%		41.10%
Met. Locations - 1 - %	29.30%	25.20%	Y	29.30%
ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan				

NAR (Cumulative Events)

All	8.8 (0.0)	8.8 (0.1)	8.4 (0.6)	7.9 (3.1)	7.9 (3.1)	5.4 (3.1)	0.9 (3.3)	0.8 (3.3)	0.0 (3.3)
Fallback	98.4 (0.0)	89.9 (9.0)	83.2 (16.7)	75.9 (23.4)	72.5 (27.3)	54.7 (27.3)	13.4 (30.0)	10.9 (30.0)	0.0 (30.0)
Primary	25.5 (0.0)	22.5 (4.1)	20.4 (5.3)	16.4 (9.2)	15.9 (9.8)	13.4 (9.8)	2.6 (11.4)	2.3 (11.4)	0.0 (11.4)
Secondary	91.1 (0.0)	84.2 (7.5)	77.9 (14.2)	70.3 (21.8)	67.3 (24.7)	50.0 (24.7)	12.8 (28.6)	10.5 (28.6)	0.0 (28.6)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 15. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RAISE Overall survival
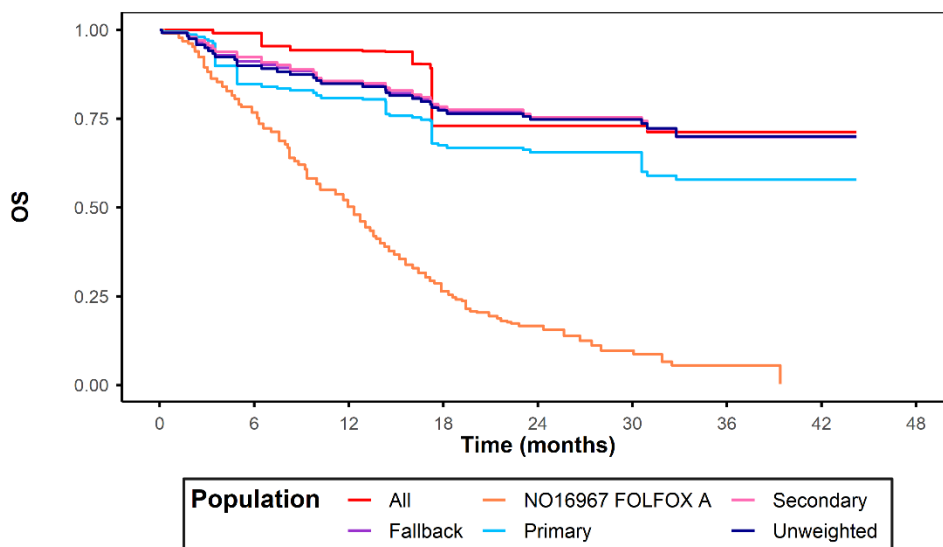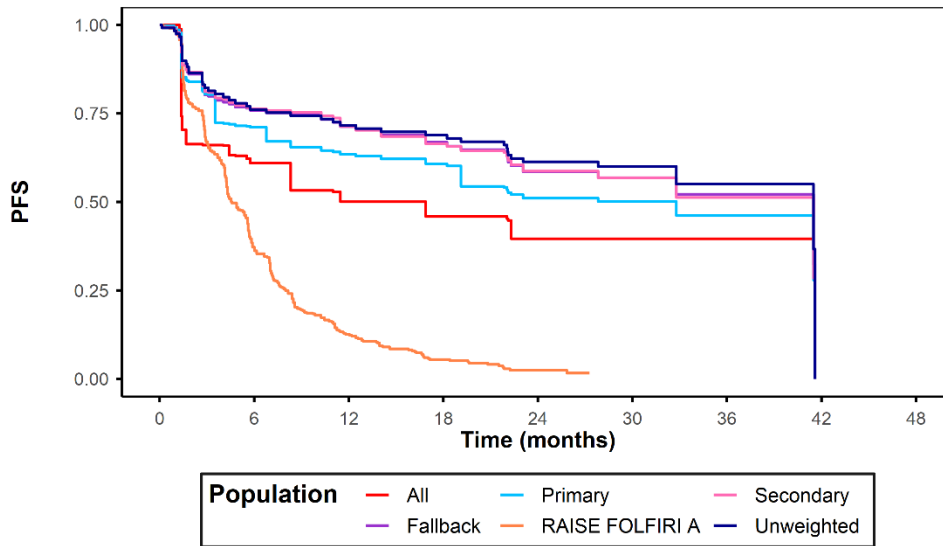
NAR (Cumulative Events)

All	8.8 (0.0)	5.2 (3.4)	4.4 (4.3)	4.2 (4.7)	3.7 (5.2)	2.6 (5.2)	0.6 (5.2)	0.0 (5.2)	0.0 (5.2)
Fallback	98.4 (0.0)	72.9 (23.5)	67.4 (27.9)	61.6 (31.8)	52.5 (39.2)	26.3 (40.2)	8.6 (41.0)	0.0 (43.0)	0.0 (43.0)
Primary	25.5 (0.0)	17.0 (7.2)	15.0 (9.0)	14.2 (9.6)	11.7 (11.8)	6.9 (12.0)	1.2 (12.1)	0.0 (12.4)	0.0 (12.4)
Secondary	91.1 (0.0)	67.3 (21.3)	63.0 (25.5)	56.3 (29.7)	48.3 (35.9)	23.2 (37.0)	8.3 (37.9)	0.0 (40.3)	0.0 (40.3)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

**Figure 16. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RAISE Progression-free survival**

Table 29: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: VELOUR

Variable	VELOUR (FOLFIRI)	CheckMate 142 Nivolumab + Ipilimumab		
	Unadjusted	Unadjusted	Matched (secondary set)	
	Value	Value	Matched?	Value
N/ESS	614	119		57.4
Age (years) - min	19	21	Y	21
Age (years) - median	61	58	Y	60.9
Age (years) - max	86	88	Y	81
Sex - Male - %	57.50%	58.80%	Y	57.50%
Race - Asian - %	8.30%	2.50%		1.60%
Race - Black - %	8.30%	1.70%		2.20%
ECOG PS - 0 - %	57.00%	45.40%		48.40%
Primary tumour location - rectum - %	28.30%	5.00%		5.80%
Met. Loc. - Liver - %	70.20%	42.90%		48.10%
Met. Loc. - Lung - %	45.10%	26.10%	Y	45.10%
Met. Loc. - Peritoneum - %	14.30%	33.60%	Y	14.30%
Met. Loc. - Lymph node - %	29.50%	62.20%	Y	29.50%
Met. Locations - 1 - %	44.10%	25.20%		30.60%
ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size; FOLFIRI: 5 fluorouracil, folinic acid and irinotecan				
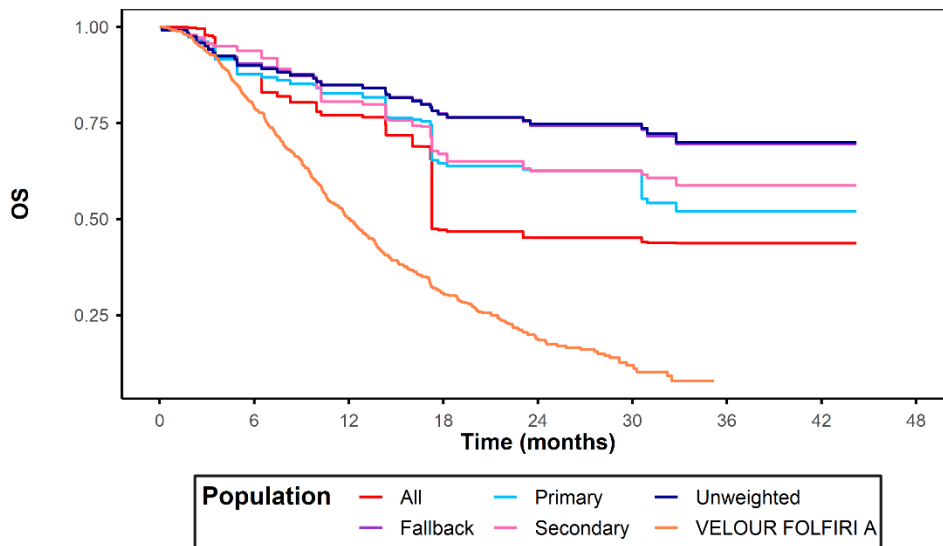
NAR (Cumulative Events)

All	17.5 (0.0)	16.0 (2.1)	13.6 (4.0)	8.3 (9.2)	7.9 (9.6)	7.2 (9.6)	2.9 (9.8)	2.8 (9.8)	0.0 (9.8)
Fallback	113.9 (0.0)	103.9 (10.8)	97.8 (17.3)	89.0 (25.7)	85.8 (29.2)	65.9 (29.2)	16.8 (32.1)	13.2 (32.1)	0.0 (32.1)
Primary	42.7 (0.0)	38.7 (5.3)	35.9 (7.4)	27.9 (15.2)	26.8 (16.0)	21.8 (16.0)	5.2 (19.0)	4.2 (19.0)	0.0 (19.0)
Secondary	57.4 (0.0)	54.2 (3.6)	48.3 (11.2)	38.8 (19.0)	36.2 (21.5)	29.7 (21.5)	8.1 (22.6)	6.4 (22.6)	0.0 (22.6)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 17. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: VELOUR Overall survival
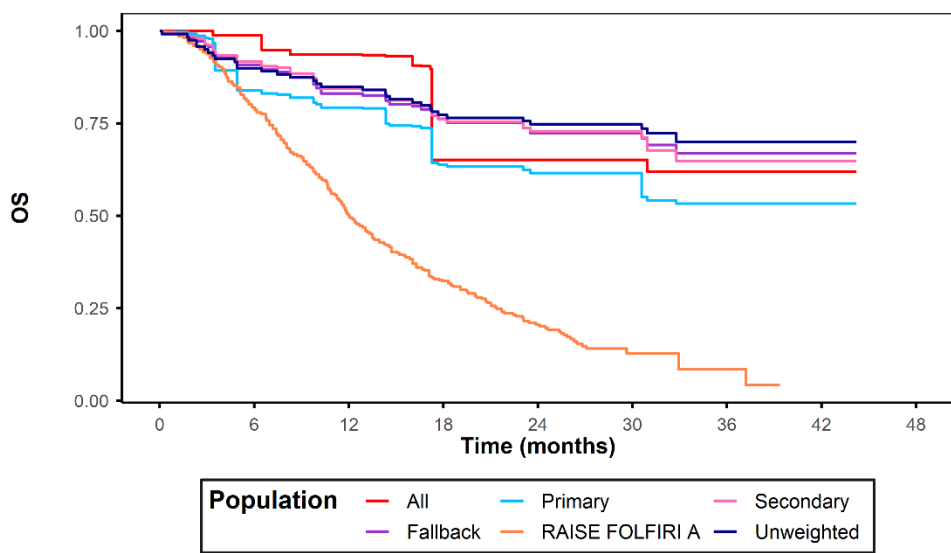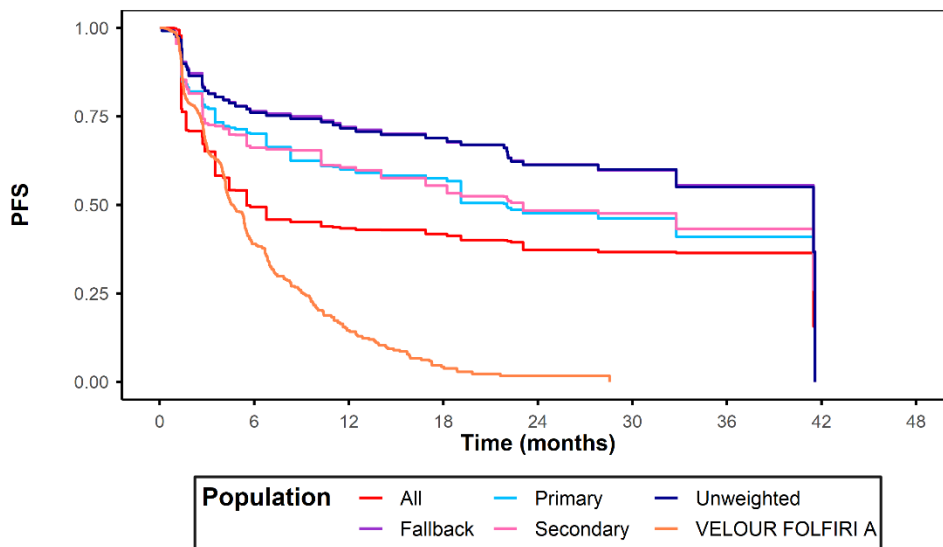

NAR (Cumulative Events)

All	17.5 (0.0)	6.6 (8.1)	5.8 (8.9)	5.7 (9.1)	5.2 (9.7)	3.5 (9.8)	1.2 (9.8)	0.0 (9.9)	0.0 (9.9)
Fallback	113.9 (0.0)	84.2 (26.5)	77.8 (31.3)	72.1 (34.5)	62.8 (42.2)	32.9 (43.3)	10.0 (44.2)	0.0 (46.5)	0.0 (46.5)
Primary	42.7 (0.0)	28.0 (12.5)	23.8 (16.5)	22.4 (17.5)	18.4 (21.3)	9.6 (21.6)	2.6 (22.0)	0.0 (22.5)	0.0 (22.5)
Secondary	57.4 (0.0)	34.8 (19.0)	31.3 (21.8)	28.9 (24.4)	24.9 (27.9)	12.1 (28.2)	4.0 (28.6)	0.0 (29.3)	0.0 (29.3)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 18. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: VELOUR progression-free survival

Trifluridine-tipiracil comparisons

Table 30: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: RECOURSE (EUR) Trifluridine-tipiracil

| Variable | RECOURSE (EUR) (Tri.-Tip.) Unadjusted | CheckMate 142 Nivolumab + Ipilimumab | | |
| | | Unadjusted | Matched (secondary set) | |
	Value	Value	Matched?	Value
N/ESS	271	119		63.2
Age (years) - mean	61.8	56.55	Y	61.8
Age (years) - sd	9.98	13.789	Y	9.98
Sex - Male - %	61.60%	58.80%	Y	61.60%
Race - Asian - %	0.40%	2.50%		0.00%
Race - Black - %	0.40%	1.70%		2.00%
ECOG PS - 0 - %	50.90%	45.40%	Y	50.90%
No. prior lines - 1 - %	0.00%	39.50%		34.80%
Region - Europe - %	100.00%	63.90%	Y	100.00%
Region - USA - %	0.00%	28.60%		0.00%
ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size				
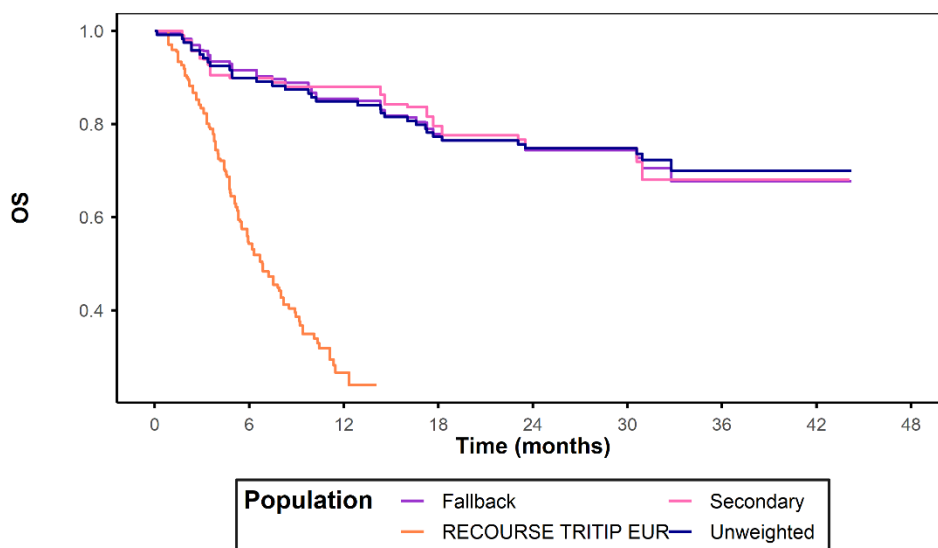
NAR (Cumulative Events)

Fallback	96.5 (0.0)	88.8 (8.1)	83.7 (14.1)	76.2 (21.4)	73.0 (24.7)	55.1 (24.7)	13.4 (28.1)	11.3 (28.1)	0.0 (28.1)
Secondary	63.2 (0.0)	57.2 (6.4)	56.2 (7.6)	51.5 (12.9)	48.4 (15.9)	37.0 (15.9)	9.3 (18.5)	7.7 (18.5)	0.0 (18.5)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 19. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RECOURSE (EUR) Trifluridine-tipiracil Overall survival

Figure 20. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RECOURSE (EUR) Trifluridine-tipiracil Progression-free survival

Table 31: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: RECOURSE (USA) Trifluridine-tipiracil

| Variable | RECOURSE (USA) (Tri.-Tip.) | CheckMate 142 Nivolumab + Ipilimumab | | |
| | Unadjusted | Unadjusted | Matched (secondary set) | |
	Value	Value	Matched?	Value
N/ESS	64	119		33.5
Age (years) - mean	60.2	56.55	Y	60.2
Age (years) - sd	11.86	13.789	Y	11.859
Sex - Male - %	48.40%	58.80%	Y	48.40%
Race - Asian - %	7.80%	2.50%		7.10%
Race - Black - %	4.70%	1.70%		3.20%
ECOG PS - 0 - %	43.80%	45.40%	Y	43.80%
No. prior lines - 1 - %	0.00%	39.50%		41.80%
Region - Europe - %	0.00%	63.90%	Y	0.00%
Region - USA - %	100.00%	28.60%		76.00%
ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size				
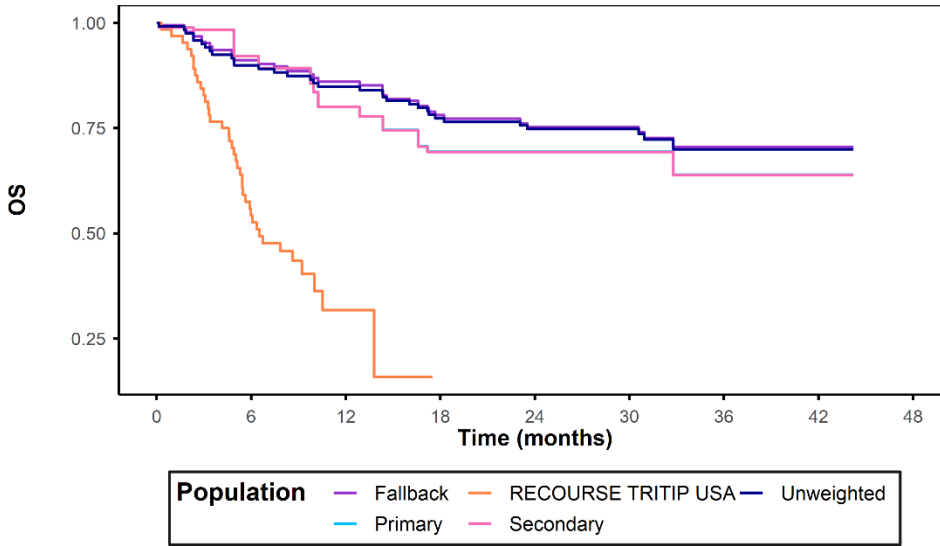
NAR (Cumulative Events)

Fallback	106.0 (0.0)	97.2 (9.4)	92.1 (14.8)	83.6 (23.2)	80.7 (26.3)	61.9 (26.3)	16.4 (28.8)	13.2 (28.8)	0.0 (28.8)
Primary	33.5 (0.0)	31.2 (2.7)	28.0 (6.7)	23.7 (10.2)	23.7 (10.2)	18.1 (10.2)	5.0 (10.9)	4.0 (10.9)	0.0 (10.9)
Secondary	33.5 (0.0)	31.2 (2.6)	28.0 (6.7)	23.7 (10.3)	23.7 (10.3)	18.1 (10.3)	5.0 (10.9)	4.0 (10.9)	0.0 (10.9)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 21. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RECOURSE (USA) Trifluridine-tipiracil Overall survival
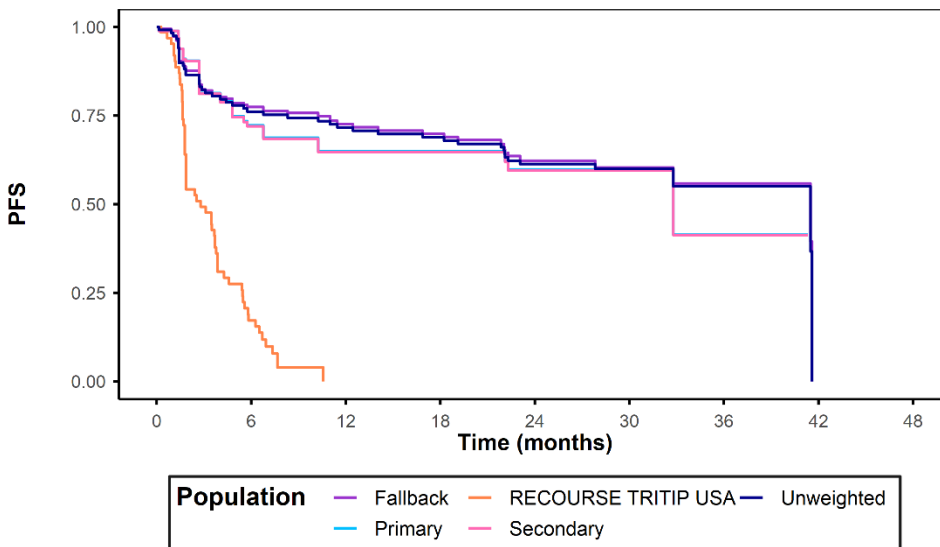
NAR (Cumulative Events)

Fallback	106.0 (0.0)	79.5 (23.6)	72.8 (28.4)	68.3 (31.1)	59.8 (38.3)	31.3 (39.7)	9.0 (40.5)	0.0 (42.7)	0.0 (42.7)
Primary	33.5 (0.0)	22.8 (8.9)	20.2 (11.2)	19.7 (11.2)	17.2 (12.6)	9.4 (12.6)	2.1 (13.3)	0.0 (13.3)	0.0 (13.3)
Secondary	33.5 (0.0)	22.8 (9.0)	20.1 (11.3)	19.6 (11.3)	17.2 (12.7)	9.3 (12.7)	2.1 (13.4)	0.0 (13.4)	0.0 (13.4)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 22. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RECOURSE (USA) Trifluridine-tipiracil Progression-free survival

Table 32: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: TERRA Trifluridine-tipiracil

Variable	TERRA (Tri.-Tip.) Unadjusted	CheckMate 142 Nivolumab + Ipilimumab		
	Value	Unadjusted Value	Matched (secondary set) Matched?	Value
N/ESS	271	119		92.5
Age (years) - min	26	21	Y	26
Age (years) - median	58	58	Y	57.3
Age (years) - max	81	88	Y	81
Sex - Male - %	62.70%	58.80%	Y	62.70%
KRAS - wild type - %	63.50%	58.10%	Y	63.50%
ECOG PS - 0 - %	23.60%	45.40%	Y	23.60%
Time from diagnosis (years) - min	0.11	0.14	Y	0.14
Time from diagnosis (years) - median	1.55	1.62	Y	1.55
Time from diagnosis (years) - max	8.9	19.6	Y	8.89
Primary tumour location - rectum - %	56.80%	5.00%		3.20%
No. prior lines - 1 - %	0.00%	39.50%		36.80%
ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size				

NAR (Cumulative Events)

All	5.7 (0.0)	5.5 (0.2)	4.9 (0.7)	3.7 (1.9)	3.4 (2.8)	2.9 (2.8)	1.1 (2.8)	0.6 (2.8)	0.0 (2.8)
Fallback	115.0 (0.0)	106.0 (10.1)	99.9 (16.1)	91.2 (24.9)	88.2 (27.8)	69.7 (27.8)	17.5 (31.0)	13.5 (31.0)	0.0 (31.0)
Primary	10.5 (0.0)	8.9 (1.7)	8.5 (2.2)	5.7 (6.0)	4.5 (6.2)	3.9 (6.2)	0.6 (6.2)	0.4 (6.2)	0.0 (6.2)
Secondary	92.5 (0.0)	84.3 (9.5)	78.2 (14.8)	75.1 (17.9)	73.5 (20.2)	61.2 (20.2)	15.9 (21.1)	12.6 (21.1)	0.0 (21.1)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 23. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: TERRA Overall survival
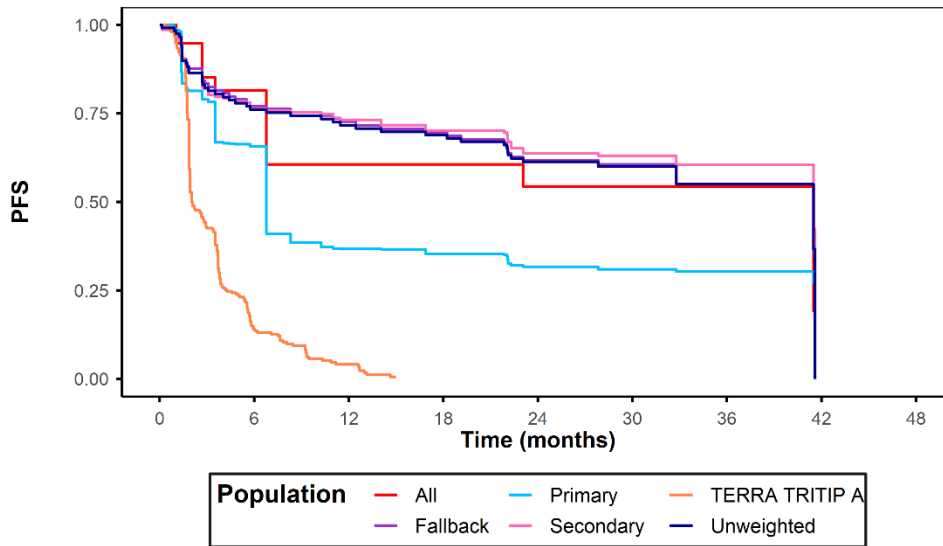
NAR (Cumulative Events)

All	5.7 (0.0)	4.6 (1.0)	3.4 (2.2)	2.9 (2.2)	2.9 (2.5)	0.8 (2.5)	0.3 (2.5)	0.0 (2.5)	0.0 (2.5)
Fallback	115.0 (0.0)	85.2 (25.9)	78.4 (30.7)	73.3 (33.9)	63.1 (41.9)	33.6 (42.8)	9.7 (43.9)	0.0 (45.8)	0.0 (45.8)
Primary	10.5 (0.0)	6.9 (3.6)	3.8 (6.6)	3.6 (6.8)	3.2 (7.1)	1.3 (7.2)	0.3 (7.2)	0.0 (7.2)	0.0 (7.2)
Secondary	92.5 (0.0)	67.4 (21.6)	62.0 (24.2)	58.7 (26.6)	51.4 (31.8)	29.0 (32.2)	8.2 (32.6)	0.0 (34.6)	0.0 (34.6)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 24. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: TERRA Progression-free survival

Best supportive care comparisons

Table 33: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: RECOURSE (EUR) BSC

Variable	RECOURSE (EUR) (BSC)	CheckMate 142 Nivolumab + Ipilimumab		
	Unadjusted	Unadjusted	Matched (secondary set)	
	Value	Value	Matched?	Value
N/ESS	132	119		64.2
Age (years) - mean	62.1	56.55	Y	62.1
Age (years) - sd	10.42	13.789	Y	10.42
Sex - Male - %	62.10%	58.80%	Y	62.10%
Race - Asian - %	0.80%	2.50%		0.00%
Race - Black - %	0.00%	1.70%		1.90%
ECOG PS - 0 - %	51.50%	45.40%	Y	51.50%
No. prior lines - 1 - %	0.00%	39.50%		35.60%
Region - Europe - %	100.00%	63.90%	Y	100.00%
Region - USA - %	0.00%	28.60%		0.00%
BSC: Best supportive care; ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size				
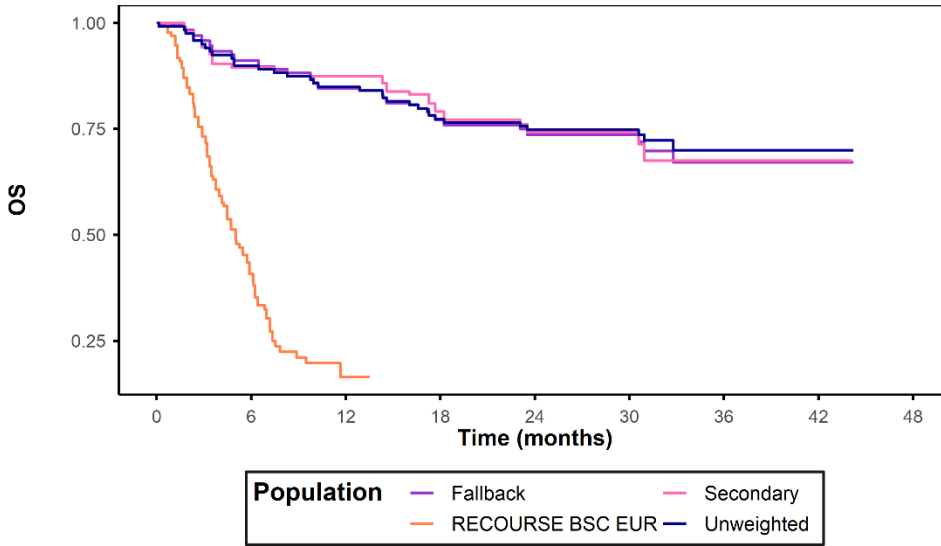
NAR (Cumulative Events)

Fallback	97.5 (0.0)	89.2 (8.7)	83.7 (15.1)	76.2 (22.3)	73.0 (25.8)	54.9 (25.8)	13.3 (29.0)	11.2 (29.0)	0.0 (29.0)
Secondary	64.2 (0.0)	58.0 (6.8)	56.8 (8.1)	51.9 (13.4)	48.8 (16.5)	37.2 (16.5)	9.2 (19.2)	7.6 (19.2)	0.0 (19.2)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 25. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RECOURSE (EUR) BSC Overall survival
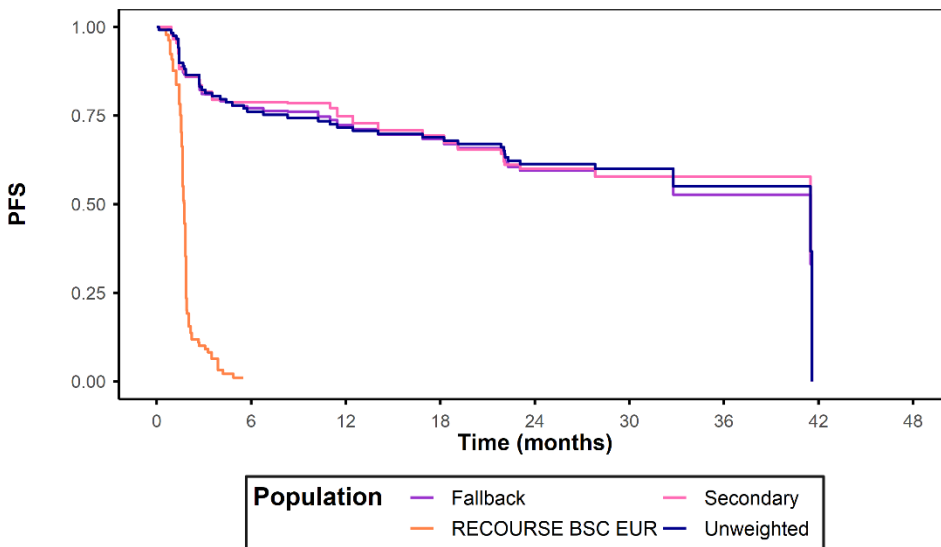
NAR (Cumulative Events)

Fallback	97.5 (0.0)	73.9 (22.1)	68.3 (26.6)	61.9 (30.1)	52.4 (37.9)	27.4 (39.0)	8.4 (39.9)	0.0 (42.2)	0.0 (42.2)
Secondary	64.2 (0.0)	50.7 (13.6)	48.2 (16.1)	43.1 (19.4)	36.9 (25.1)	19.9 (26.2)	6.6 (26.2)	0.0 (28.3)	0.0 (28.3)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 26. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RECOURSE (EUR) BSC Progression-free survival

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Table 34: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: RECOURSE (USA) BSC

| Variable | RECOURSE (USA) (BSC) Unadjusted | CheckMate 142 Nivolumab + Ipilimumab | | |
| | | Unadjusted | Matched (secondary set) | |
	Value	Value	Matched?	Value
N/ESS	35	119		36.1
Age (years) - mean	58.5	56.55	Y	58.5
Age (years) - sd	11.02	13.789	Y	11.021
Sex - Male - %	51.40%	58.80%	Y	51.40%
Race - Asian - %	8.60%	2.50%		8.00%
Race - Black - %	14.30%	1.70%		4.30%
ECOG PS - 0 - %	37.10%	45.40%	Y	37.10%
No. prior lines - 1 - %	0.00%	39.50%		43.60%
Region - Europe - %	0.00%	63.90%	Y	0.00%
Region - USA - %	100.00%	28.60%		77.80%
BSC: Best supportive care; ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size				

NAR (Cumulative Events)

Fallback	106.4 (0.0)	98.6 (8.5)	94.1 (13.0)	85.3 (22.2)	82.6 (24.6)	64.9 (24.6)	17.2 (27.6)	13.8 (27.6)	0.0 (27.6)
Primary	36.1 (0.0)	34.2 (2.5)	30.8 (6.0)	26.9 (9.4)	26.9 (9.4)	22.4 (9.4)	6.5 (10.1)	5.2 (10.1)	0.0 (10.1)
Secondary	36.1 (0.0)	34.2 (2.5)	30.8 (6.0)	27.0 (9.4)	27.0 (9.4)	22.4 (9.4)	6.5 (10.2)	5.2 (10.2)	0.0 (10.2)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 27. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RECOURSE (USA) BSC Overall survival
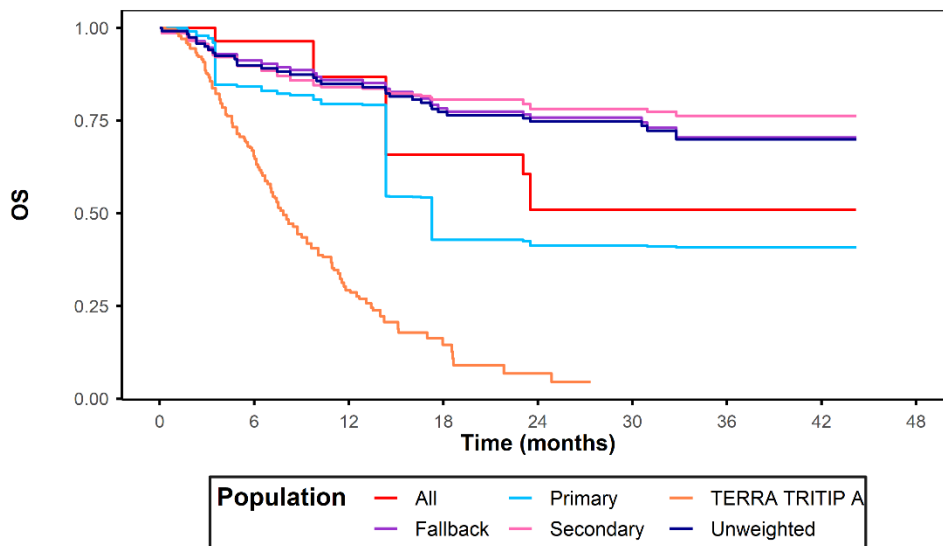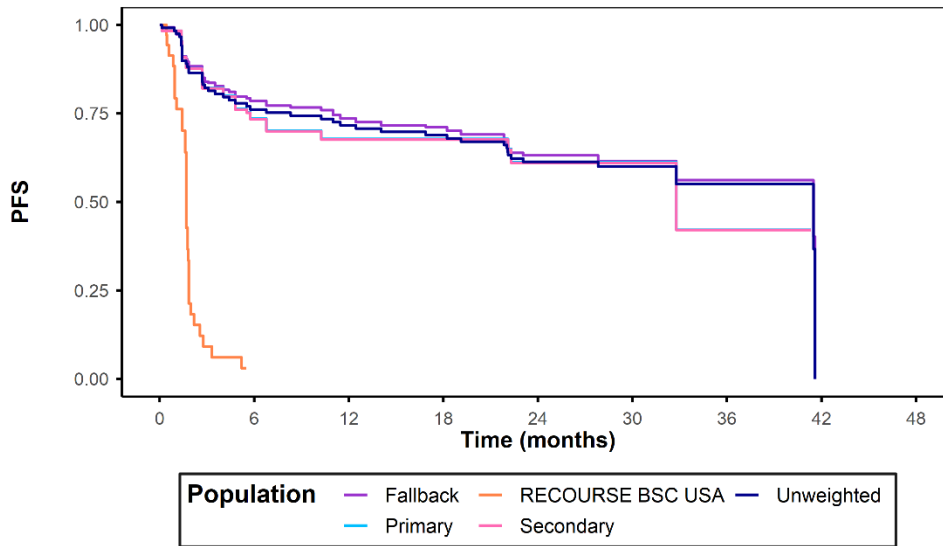
NAR (Cumulative Events)

Fallback	106.4 (0.0)	80.9 (22.4)	73.9 (27.5)	69.3 (29.8)	60.0 (37.5)	33.1 (38.6)	9.2 (39.6)	0.0 (41.9)	0.0 (41.9)
Primary	36.1 (0.0)	24.7 (9.1)	22.2 (11.0)	21.4 (11.0)	18.6 (12.8)	10.6 (12.8)	2.3 (13.6)	0.0 (13.6)	0.0 (13.6)
Secondary	36.1 (0.0)	24.7 (9.1)	22.2 (11.0)	21.3 (11.0)	18.6 (12.9)	10.5 (12.9)	2.4 (13.6)	0.0 (13.6)	0.0 (13.6)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 28. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: RECOURSE (USA) BSC Progression-free survival

Table 35: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: TERRA BSC

Variable	TERRA (BSC)	CheckMate 142 Nivolumab + Ipilimumab		
	Unadjusted	Unadjusted	Matched (secondary set)	
	Value	Value	Matched?	Value
N/ESS	135	119		85.1
Age (years) - min	24	21	Y	26
Age (years) - median	56	58	Y	55.6
Age (years) - max	80	88	Y	80
Sex - Male - %	62.20%	58.80%	Y	62.20%
KRAS – wild type - %	63.00%	58.10%	Y	63.00%
ECOG PS - 0 - %	22.20%	45.40%	Y	22.20%
Time from diagnosis (years) - min	0.12	0.14	Y	0.14
Time from diagnosis (years) - median	1.94	1.62	Y	1.92
Time from diagnosis (years) - max	8.58	19.6	Y	8
Primary tumour location - rectum - %	37.00%	5.00%		2.10%
No. prior lines - 1 - %	0.00%	39.50%		36.30%
BSC: Best supportive care; ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size				

NAR (Cumulative Events)

All	13.0 (0.0)	10.5 (2.7)	10.1 (2.9)	8.8 (4.2)	8.5 (4.5)	8.2 (4.5)	2.3 (4.6)	1.1 (4.6)	0.0 (4.6)
Fallback	111.6 (0.0)	102.7 (10.1)	97.8 (14.7)	89.4 (23.1)	86.9 (25.6)	69.3 (25.6)	17.7 (28.5)	13.4 (28.5)	0.0 (28.5)
Primary	20.8 (0.0)	17.1 (3.8)	16.6 (4.2)	12.8 (9.1)	11.5 (9.2)	10.1 (9.2)	2.3 (9.4)	1.2 (9.4)	0.0 (9.4)
Secondary	85.1 (0.0)	77.2 (9.4)	72.4 (13.0)	69.8 (15.6)	68.3 (17.7)	57.3 (17.7)	15.6 (18.5)	12.1 (18.5)	0.0 (18.5)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 29. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: TERRA BSC Overall survival
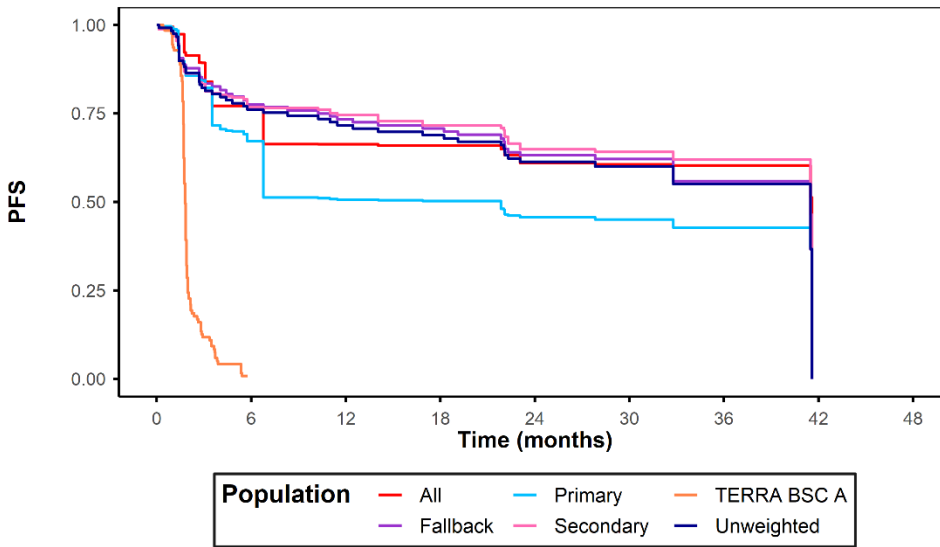
NAR (Cumulative Events)

All	13.0 (0.0)	9.8 (2.9)	8.4 (4.3)	7.6 (4.4)	7.2 (4.9)	3.5 (4.9)	0.5 (4.9)	0.0 (5.0)	0.0 (5.0)
Fallback	111.6 (0.0)	82.9 (24.6)	76.1 (29.0)	71.8 (31.6)	62.3 (39.1)	34.0 (39.8)	9.6 (41.0)	0.0 (42.7)	0.0 (42.7)
Primary	20.8 (0.0)	13.9 (6.7)	9.8 (10.1)	9.7 (10.1)	8.7 (11.0)	4.9 (11.1)	1.1 (11.2)	0.0 (11.2)	0.0 (11.2)
Secondary	85.1 (0.0)	62.4 (19.3)	57.4 (21.1)	54.5 (23.3)	48.1 (28.2)	27.8 (28.6)	8.2 (29.0)	0.0 (30.9)	0.0 (30.9)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 30. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: TERRA BSC Progression-free survival

Table 36: Adjustment of CheckMate 142 NIVO+IPI aggregate variables: LUME-Colon 1

Variable	LUME-Colon 1 (BSC) Unadjusted	CheckMate 142 Nivolumab + Ipilimumab		
		Unadjusted	Matched (secondary set)	
	Value	Value	Matched?	Value
N/ESS	382	119		79.5
Age (years) - min	23	21	Y	26
Age (years) - median	62	58	Y	61.6
Age (years) - max	83	88	Y	81
Sex - Male - %	57.10%	58.80%	Y	57.10%
Race - Asian - %	27.20%	2.50%		1.50%
KRAS - wild type - %	46.10%	58.10%	Y	46.10%
ECOG PS - 0 - %	37.20%	45.40%	Y	37.20%
Primary tumour location - rectum - %	40.30%	5.00%		5.70%
No. prior lines - 1 - %	0.00%	39.50%		34.50%
Met. Loc. - Liver - %	69.60%	42.90%	Y	69.60%
Met. Locations - 1 - %	16.50%	25.20%		16.70%
BSC: Best supportive care; ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size				
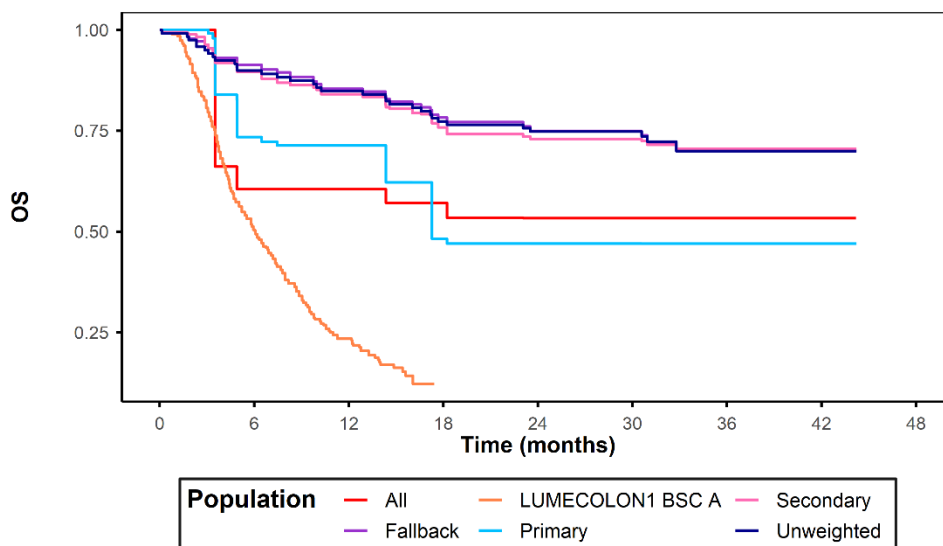
NAR (Cumulative Events)

All	4.4 (0.0)	2.7 (1.8)	2.7 (1.8)	2.5 (1.9)	2.4 (2.1)	2.1 (2.1)	1.9 (2.1)	1.9 (2.1)	0.0 (2.1)
Fallback	110.2 (0.0)	101.4 (9.6)	95.3 (16.1)	87.0 (23.9)	83.8 (27.6)	63.7 (27.6)	16.6 (30.4)	13.1 (30.4)	0.0 (30.4)
Primary	13.0 (0.0)	10.7 (3.4)	9.2 (3.7)	6.2 (6.7)	6.1 (6.9)	5.8 (6.9)	2.0 (6.9)	2.0 (6.9)	0.0 (6.9)
Secondary	79.5 (0.0)	71.7 (8.3)	67.7 (12.7)	61.1 (19.2)	58.5 (21.5)	46.2 (21.5)	14.9 (22.6)	13.5 (22.6)	0.0 (22.6)
Unweighted	119.0 (0.0)	108.0 (12.0)	102.0 (18.0)	93.0 (27.0)	90.0 (30.0)	71.0 (30.0)	18.0 (33.0)	14.0 (33.0)	0.0 (33.0)

Figure 31. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: LUME-Colon 1 Overall survival
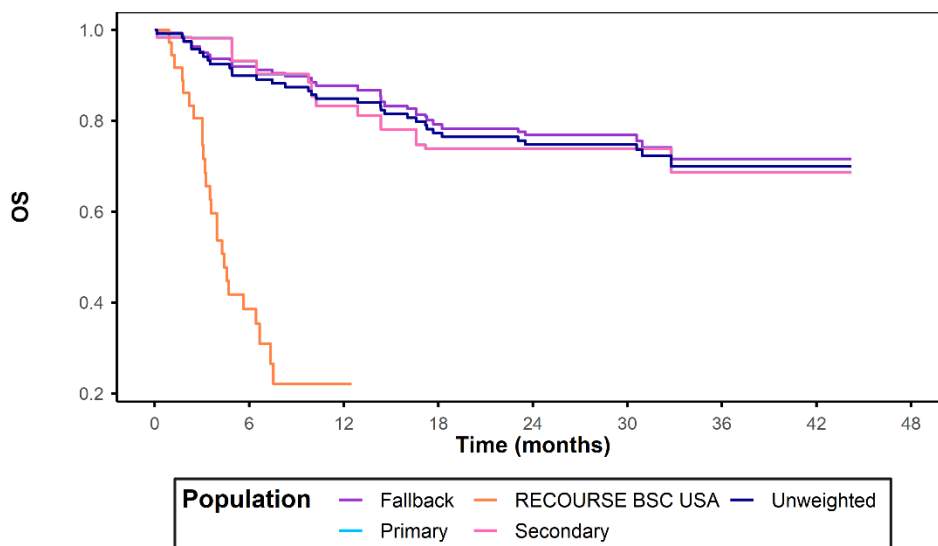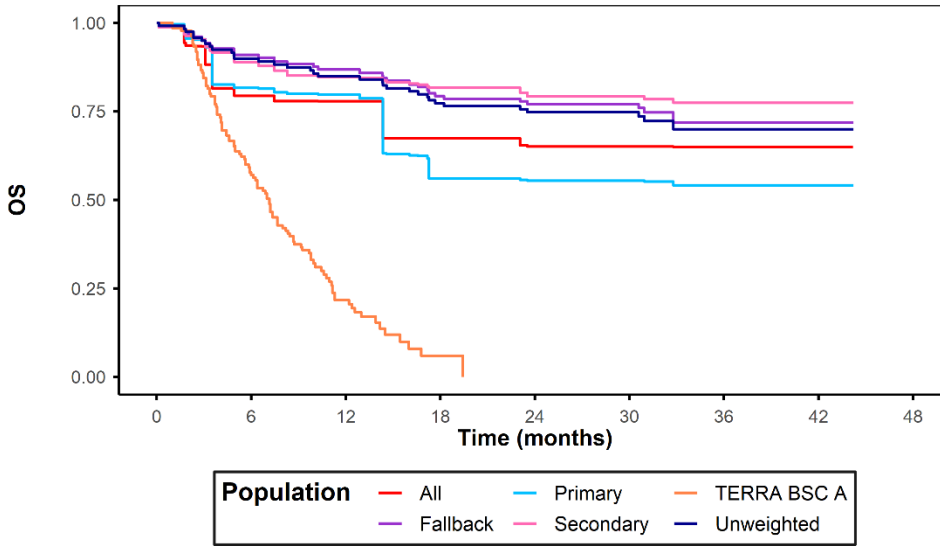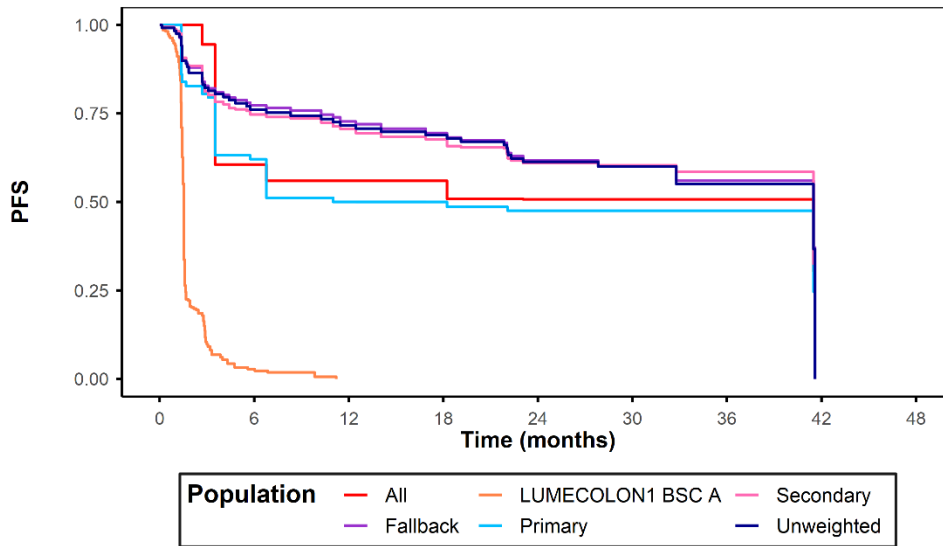
NAR (Cumulative Events)

All	4.4 (0.0)	2.7 (1.8)	1.8 (1.9)	1.8 (1.9)	1.6 (2.1)	1.2 (2.1)	0.0 (2.1)	0.0 (2.1)	0.0 (2.1)
Fallback	110.2 (0.0)	82.4 (24.7)	76.1 (29.5)	70.3 (32.7)	61.2 (40.3)	31.7 (41.5)	10.0 (42.3)	0.0 (44.8)	0.0 (44.8)
Primary	13.0 (0.0)	6.9 (4.6)	5.4 (5.9)	5.4 (5.9)	5.0 (6.1)	3.7 (6.1)	0.4 (6.1)	0.0 (6.5)	0.0 (6.5)
Secondary	79.5 (0.0)	56.2 (19.7)	52.1 (22.7)	48.0 (24.8)	41.6 (29.4)	23.6 (29.8)	9.3 (30.1)	0.0 (34.6)	0.0 (34.6)
Unweighted	119.0 (0.0)	87.0 (28.0)	80.0 (33.0)	75.0 (36.0)	65.0 (44.0)	35.0 (45.0)	10.0 (46.0)	0.0 (48.0)	0.0 (48.0)

Figure 32. Adjustment of CheckMate 142 NIVO+IPI Kaplan-Meier: LUME-Colon 1 Progression-free survival

Economic analysis using updated MAIC

As can be seen in Table 37, despite changing comparator studies and adjusting for additional covariates, the cost-effectiveness outcomes are similar. This is also reflected in the PSA analysis with probability of cost-effectiveness at 100% for all comparisons.

Scenario analyses are provided in Table 39 using alternative efficacy sources and demonstrates that outcomes remain comparable to the base case analysis, even where obvious spurious results are applied, such as the comparison with FOLFIRI from NCT01479465.

Table 37. Base case results based on updated MAIC

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£17,866	1.239	0.870	■	■	■	**£13,783**
BSC	£10,586	0.880	0.615	■	■	■	**£14,428**
FOLFOX	£11,668	1.171	0.832	■	■	■	**£14,793**
FOLFIRI	£12,204	1.728	1.227	■	■	■	**£15,810**

Table 38. PSA results based on updated MAIC

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Probability of cost-effectiveness
Trifluridine-tipiracil								
NIVO+IPI	■	■	■	-	-	-	-	-
Trifluridine-tipiracil	£17,997	1.268	0.891	■	■	■	**£13,585**	■
BSC								
NIVO+IPI	■	■	■	-	-	-	**-**	**-**
BSC	£10,609	0.913	0.639	■	■	■	**£14,254**	■
FOLFOX								
NIVO+IPI	■	■	■	-	-	-	-	-
FOLFOX	£11,610	1.189	0.846	■	■	■	**£14,596**	■
FOLFIRI								
NIVO+IPI	■	■	■	-	-	-	**-**	**-**
FOLFIRI	£11,495	1.748	5.314	■	■	■	**£15,708**	■
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc.: incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years								

■

Figure 33. DSA tornado: NIVO+IPI versus trifluridine-tipiracil based on updated MAIC

■

Figure 34. DSA tornado: NIVO+IPI versus BSC based on updated MAIC

■

Figure 35. DSA tornado: NIVO+IPI versus FOLFOX based on updated MAIC

■

Figure 36. DSA tornado: NIVO+IPI versus FOLFIRI based on updated MAIC

Table 39. Scenario analysis results based on updated MAIC

Comparator	Study	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Trifluridine-tipiracil	RECOURSE USA	■	■	**£13,435**
	TERRA*	■	■	**£13,133**
BSC	RECOURSE USA	■	■	**£14,177**
	LUME-Colon-1	■	■	**£14,339**
	TERRA*	■	■	**£14,101**
FOLFOX	NO16967	■	■	**£14,670**
	CAPRI-GOIM*	■	■	**£15,619**
FOLFIRI	RAISE	■	■	**£15,379**
	NCT01479465**	■	■	**£18,457**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years * Reflects the most optimistic outcomes for comparators				

c) **For the BSC comparator, the ERG notes that the full-text paper of LUME-Colon 1 does not appear in the company's data extraction sheet. This full text paper reports the proportion of patients who were KRAS-wildtype or had a KRAS mutation which could be used as a variable in the MAIC. Please consider this paper when re-assessing the studies in line with the above criteria.**

LUME-Colon 1 was included in the data extraction grid as study number 225 (Van Cutsem 2016[30]) and is reflected in the SLR report summary of BSC data.

LUME-Colon 1 and RECOURSE enrolled similar patient population and achieved comparable outcomes. However, LUME-Colon 1 was not originally included in the MAIC, as it reflected slightly more treatment experienced patients and reflects a clinical pathway that may not be relevant to the UK setting: over a third of patients received previous regorafenib and patients had also previously received trifluridine-tipiracil. As RECOURSE provided similar OS KM and included a relevant comparator arm, which was not available from LUME-Colon 1, RECOURSE was considered to be more appropriate for inclusion. However, LUME-Colon 1 has been considered as a scenario analysis in response to these clarification questions. Further, proportion of patients with KRAS mutations have been assessed for both RECOURSE and LUME-Colon 1.

A12. Priority question: In NICE DSU Technical Support Document (TSD) 18 the recommendation is that "For an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables." In order to provide the most accurate (although less precise) estimate for each of the comparisons, please present the results for FOLFOX, FOLFIRI, trifluridine-tipiracil, and BSC using the covariate set adjusting for all potentially prognostic factors. Please use the studies based on the re-assessment of the comparator studies in response to question A11.

Outcomes are provided in Table 40 (OS) and Table 41 (PFS). As can be observed, the effective study size is very low across all analyses, with no comparison an effective study size greater than 20 patients. This has a commensurate impact on outcomes, with a number of spurious results provided that lack clinical plausibility or face validity. In particular, the low effective study size indicates high concentration of patient weights in few individuals who are members of poorly sampled subgroups, such as 6 patients with rectal tumour location.

Table 40. MAIC output: Overall survival outcomes applying all covariates

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)		ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	Original
CheckMate 142	NIVO+IPI	119	168.13	5.12 (0.177)							
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	All	18.6	173.7	5.16 (0.319)	2.31 (0.322)	16.76	15.65
NO16967	Scenario	314	13.96	2.64 (0.042)	All	12.8	162.9	5.09 (0.431)	2.46 (0.433)	14.41	NA
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	All	6.4	97.2	4.58 (0.693)	1.52 (0.703)	36.64	NA
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	All	8.8	120.4	4.79 (NA)	2.00 (NA)	22.66	17.19
VELOUR	Base case	614	15.70	2.75 (0.046)	All	17.5	82.9	4.42 (0.279)	1.66 (0.282)	31.82	15.30
NCT01479465	Scenario	80	20.97	3.04 (0.164)	All	18.2	90.6	4.51 (0.378)	1.46 (0.412)	38.91	NA
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	All	NA	NA	NA	NA	NA	10.86
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	All	NA	NA	NA	NA	NA	11.70
TERRA	Scenario	271	11.60	2.45 (0.066)	All	5.7	60.5	4.10 (0.805)	1.65 (0.808)	32.22	NA
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	All	NA	NA	NA	NA	NA	7.55
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	All	NA	NA	NA	NA	NA	8.13
LUME-Colon 1	Scenario	382	10.24	2.33 (0.129)	All	4.4	141.4	4.95 (0.679)	2.63 (0.691)	12.18	NA
TERRA	Scenario	135	8.70	2.16 (0.072)	All	13.0	147.8	5.00 (0.537)	2.83 (0.542)	9.90	NA

BSC: best supportive care; ESS: effective sample size; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 41. MAIC output: Progression-free survival outcomes applying all covariates

Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	Original
CheckMate 142	NIVO+IPI	119	69.8	4.25 (0.185)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	All	18.6	76.1	4.33 (0.392)	2.63 (0.394)	5.02	7.54
NO16967	Scenario	314	5.36	1.68 (0.041)	All	12.8	32.0	3.47 (0.540)	1.79 (0.542)	11.68	NA
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	All	6.4	25.0	3.22 (0.673)	1.32 (0.683)	18.70	NA
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	All	8.8	37.2	3.62 (NA)	1.73 (NA)	12.42	6.33
VELOUR	Base case	614	6.79	1.92 (0.047)	All	17.5	41.0	3.71 (0.289)	1.80 (0.293)	11.56	4.49
NCT01479465	Scenario	80	8.17	2.10 (0.121)	All	18.2	52.6	3.96 (0.434)	1.86 (0.450)	10.85	NA
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	All	NA	NA	NA	NA	NA	4.19
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	All	NA	NA	NA	NA	NA	3.70
TERRA	Scenario	271	3.99	1.38 (0.715)	All	5.7	40.9	3.71 (1.133)	2.33 (1.340)	6.81	NA
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	All	NA	NA	NA	NA	NA	2.10
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	All	NA	NA	NA	NA	NA	1.90
LUME-Colon 1	Scenario	382	1.88	0.63 (0.226)	All	4.4	74.6	4.31 (1.013)	3.68 (1.038)	1.76	NA
TERRA	Scenario	135	1.97	0.68 (0.034)	All	13.0	65.2	4.18 (0.735)	3.50 (0.736)	2.11	NA

BSC: best supportive care; ESS: effective sample size; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

A13. Priority question: Please provide further details on "transporting" the survival estimates for comparators back to the CheckMate 142 ITT population.

a) The statement, "Transport the relative treatment effect onto the population of interest, represented by CheckMate 142." implies this is done using a relative treatment effect as advocated in NICE DSU TSD 18 assuming "conditional constancy of relative effects". If this is the case, please provide more details on how this was carried out, explicitly describing what the relative treatment effect estimate was and how it was implemented in the model.

b) The rest of the text in the company submission leads the ERG to infer that an absolute difference in mean survival from the MAIC has been utilised in their comparison with the Checkmate 142 ITT population. If this is the case, please can the company justify using an "assumption of conditional constancy of absolute effects" despite NICE DSU TSD 18 stating that, "This assumption is very strong (if not implausibly so)."

As stated in Company Submission Section B.2.1.1.1.1, relative treatment effects were applied to transport the treatment effect onto the population of interest, represented by CheckMate 142. The methods for this were as follows:

- Following selection of relevant evidence for each comparator, OS and PFS Kaplan-Meier data were digitised and parametric extrapolations were derived to provide estimates of mean survival.

- Mean outcomes for the comparator were converted to the log scale.

- Mean outcomes from the adjusted NIVO+IPI arm (i.e., MAIC output) were converted to the log scale.

- The difference between the log mean outcomes was calculated and used as the basis of the relative treatment effect.

- The relative treatment effect (log mean difference) was applied to the unadjusted NIVO+IPI log mean outcome to derive an adjusted log mean for the comparator.

The difference in log mean outcomes is applied directly within the economic model, used against the log mean outcome in the NIVO+IPI arm.

In reference to the ERG's question, the difference in log mean survival is a relative value, i.e., the log of the ratio of mean survivals, not an absolute value, and hence aligns to NICE DSU TSD 18.

A14. Please confirm if the results presented in Table 14 of Document B are pooled results of all included studies for each comparator. Please specify which studies were pooled for each comparator, provide the rationale for pooling the results across all comparator studies, and provide the methods for pooling the data.

Company submission Table 14 presents pooled results from all studies for each comparator, as outlined in the clinical SLR report (Appendix D); no studies were excluded. These outcomes were weighted by patient numbers for each study.

As outlined in Company submission Figure 12–Figure 14, there was significant spread for each outcome, but most data points are centralised around a smaller range. Further, the SLRs included RCTs as well as observational and single-arm studies, and the robustness may vary between these studies. When observational and single-arm studies are excluded, RCT evidence provided a tighter range of outcomes for each endpoint of interest. For this reason, it is informative to run scenario analyses in the economic model using specific relevant studies. However, it is also informative to use the overall available evidence. Hence, an additional economic scenario analysis is provided using the pooled results from the SLR, as replicated in this document as Table 48.

A15. Please specify the number of patients excluded from Checkmate 142 before matching for each comparison, and for what patient characteristic(s) there was no overlap between the studies and were therefore excluded.

In line with the stated process, CheckMate 142 patients were assessed for overlap with the comparator study to ensure that patients could potentially have been enrolled within the comparator study. In particular, patients were assessed in reference to stated eligibility criteria; if patients would not have been eligible for the comparator study, then zero weight would have been applied and those patients would not have informed subsequent outcomes. However, in the presented comparisons, no patients were specifically excluded.

A16. Please comment on the clinical plausibility of the mean OS figure of ▉▉ months for NIVO+IPI generated from the indirect treatment comparison.

As described in the Company Submission, NIVO+IPI mean OS of ▉▉ months is an input from the survival analysis rather than an output generated by the indirect treatment comparison.

NIVO+IPI patient-level data from CheckMate 142 is weighted to match the comparator study population summary statistics, with NIVO+IPI mean outcomes adjusted based on that weighting. These NIVO+IPI outcomes are used to derive a relative treatment effect versus the comparator, which is used to transport the treatment effect onto the population of interest, represented by CheckMate 142. Adjusted mean survival outcomes for NIVO+IPI are presented in Table 31 and Table 32 of Appendix L.

The mean OS for NIVO+IPI was derived using the extrapolation methods outlined in Appendix M. As can be observed, all extrapolations for NIVO+IPI predict mean OS outcomes ████████ months within the CheckMate 142 population when evaluated in a relative survival framework using national lifetables. Of the semi-parametric models assessed, only two provided lower estimates of mean OS: exponential, which provided mean OS of ████ months but was a visibly poor fit to the data; and Weibull, which provided mean OS of ████ months and provided an adequate fit to the data but was not as well fitted as the log-logistic fit. However, log-logistic was not the best fit to the observed data: using goodness-of-fit statistics and visual assessment, Gompertz was the best fitting parametric model, but was excluded due the optimistic mean OS predicted (████ months). To note, the Gompertz model predicted the additional follow-up data (page 2) better than other models, but at the point of deciding upon these models, the company acknowledged the uncertainty in the long-term outcomes and considered the log-logistic model to be a conservative base case estimate to allow for decision making without the assumption of long-term zero excess hazard implied by the Gompertz hazard profile.

Clinicians were consulted regarding their opinion upon the long-term survival and progression-free survival of patients in this subgroup receiving treatment with NIVO+IPI.[44] In these discussions, clinicians expressed an expectation that a large proportion of patients without progression at 2 years would be surviving at 5 years, and that durable response may be expected to continue for an indefinite period, with no evidence to suggest that this would be less than 5 years, especially in a young population with few comorbidities and lower risk of immune-related AEs.

Within the economic model, the disease-specific excess hazard of the log-logistic model is added to general population ACM hazard from lifetables. When this is applied (as documented in Table 66, approximately half (51.7%) of the patients are dead at ten years from baseline (i.e., 66.6 years) using the semi-parametric log-logistic function; around a third (33.6%) of patients remain alive at twenty years from baseline (i.e., 76.6 years).

Further, in the context of the observed outcomes, NIVO+IPI mean survival of ████ months can be considered plausible. Based on the database lock presented in the Company submission, median OS was ████████ and OS at 30 months was ████. In the updated database lock presented within this document, median OS has ██████████████ and OS at five years remains at approximately ██, with only ██ additional death events in the updated follow-up. Hence, 51.7% of patients remaining alive at ten years may be considered conservative.

A17. Please further justify why the following potential covariates were not considered: number of metastatic sites, proportion of patients with liver / intraperitoneal metastases.

In the initially submitted analyses, number of metastatic sites and proportion of patients with liver/intraperitoneal metastases were not assessed due to inconsistent reporting. However, these are

included in the updated analyses provided in response to Question A11 and demonstrate limited impact on outcomes.

A18. Given that a large proportion of patients in Checkmate 142 had treatments that are not used in NHS clinical practice (e.g. bevacizumab) prior to entry into the trial (and as a subsequent therapy in some patients), please comment on the extent to which this may bias the results of the indirect treatment comparison.

Bevacizumab use is high across published RCTs for previously treated mCRC. Although bevacizumab use was not reported for MAIC studies reporting FOLFOX use, bevacizumab was heavily used is studies reporting use of other comparators, including:

- FOLFIRI:
    - RAISE[9]: eligibility criteria required first-line combination therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine for metastatic disease.
    - VELOUR[8]: prior bevacizumab was received in 30.5% of patients.
- Trifluridine/tipiracil and BSC:
    - RECOURSE[27]: 799 of 800 patients had received prior bevacizumab.
    - TERRA[28]: 28% of trifluridine/tipiracil patients and 33% of placebo patients had received an anti-VEGF inhibitor.
- BSC
    - LUME-colon 1[30]: 96.9% of placebo patients had received bevacizumab and 99.7% had received bevacizumab or aflibercept.

It is acknowledged that over half of patients in the CheckMate 142 overall population (57.0%) had previously received a VEGF inhibitor,[45] which is not a recommended treatment option in the UK.[46] However, there is no evidence to suggest that NIVO+IPI would be less efficacious in patients who had not received these therapies. While patients who are more heavily pre-treated are more likely to be resistant to subsequent therapy,[47] the response rate during CheckMate 142 remained consistent between patient subgroups, including subgroups based on number of prior therapies.

Hence, in the context of the treatment history for comparator evidence and the efficacy profile of NIVO+IPI, prior use of bevacizumab is unlikely to bias the ITC.

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please update the economic analyses based on the responses to questions A11 and A12. Please indicate what other assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses. Results only need to be provided for comparisons with trifluridine-tipiracil, FOLFIRI, FOLFOX and BSC. Please provide all requested scenario analyses as executable options in the economic model. Additional models will be accepted if there is a large computational burden from including all scenarios in the same model.

Please see Question A11.Outcomes provided in response to question A12 have not been applied in the economic model, as these comparator outcomes lack face validity due to low effective study size.

Survival analysis

B2. Priority question: For NIVO+IPI, please explain why a semi-parametric log-logistic distribution was considered plausible to inform the base case analysis when its predictions for OS are above all-cause mortality (ACM).

The model combines mortality as estimated from the trial Kaplan-Meier data, in the base using a semi-parametric log-logistic function. To account for increasing general population mortality, general population mortality is also applied from the point at which the parametric function is utilised (cycle 29). The two survival functions are combined multiplicatively. As such, the modelled survival curve is never above all-cause mortality.

It should be noted that the model trace reflects both OS alone and OS with ACM, which may have caused contributed to confusion. However, Figure 37 compares three sets of model output: general population mortality estimates, the unadjusted semi-parametric survival function and the final adjusted survival model applied in the health state occupancy trace.

Overall plausibility of this survival curve is discussed in response to Question A16.

100 — General population mortality
- - - OS curve (semi-parametric log-logistic)
· · · · · OS curve after general population mortality adjustment (model output)
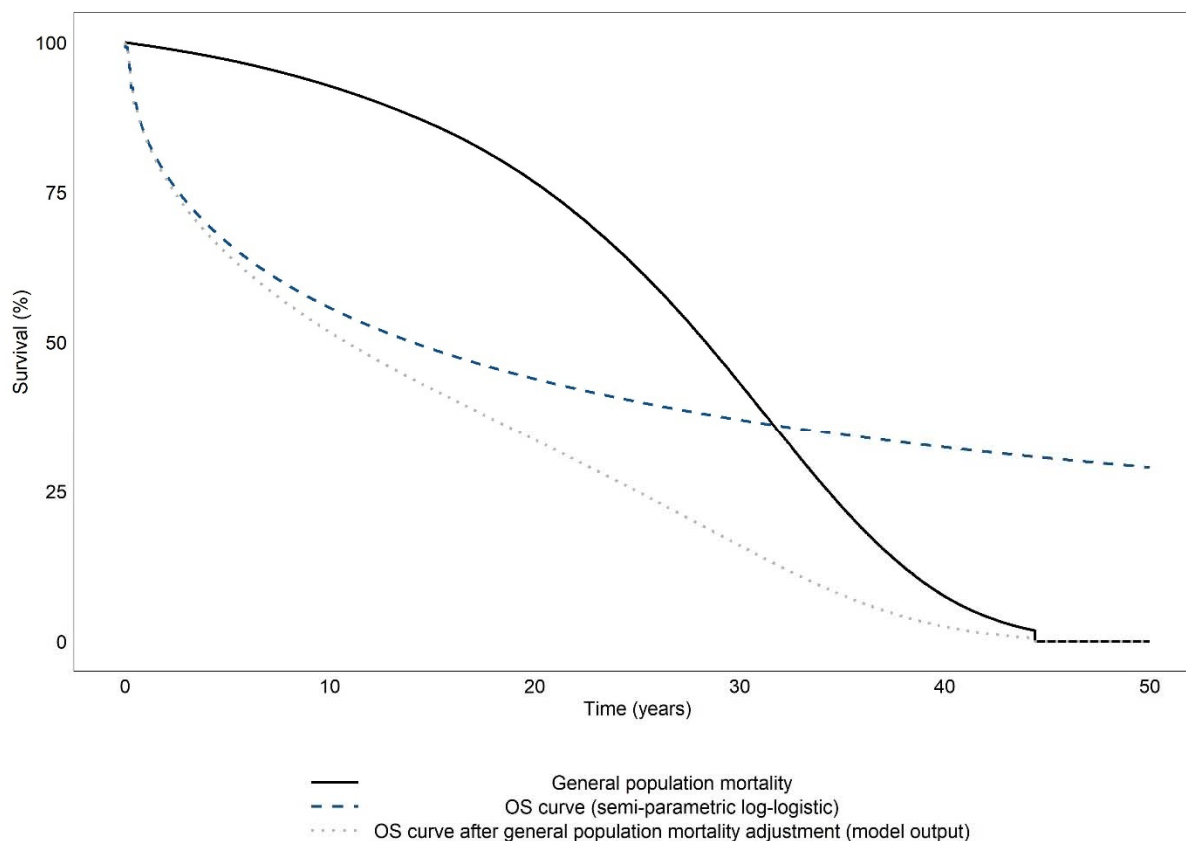
Figure 37. Comparison of modelled survival profiles (NIVO+IPI)

General population mortality is curtailed at age 100 years, causing a distortion at approximately 44 years.

B3. Priority question: Please add the fully parametric models used to inform Table 53 of Document B as profiles to model PFS, OS and time on treatment to the economic model. Only the semi-parametric models have currently been included.

With the exception of survival profiles which demonstrated a significant lack of fit to the underlying Kaplan-Meier data (as described in Document B, Section B.3.3.2.), all fully parametric survival models for PFS, OS and time on treatment are provided. Please refer to the model entitled "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking" and the relevant survival profile dropdown menus on the 'Model Control' worksheet. Alongside these clarifications, we have provided an additional user guide document to provide additional clarity with respect to the practical use of the model.

B4. Priority question: For NIVO+IPI, please explore spline-based models for PFS and time to treatment discontinuation (TTD). Use the advice in NICE DSU TSD 21 to help inform the number and location of the knots.

The placement of 0 to 7 internal knots was assessed for the distributions fit to PFS and ToT. For each model with internal knots, the location and value of these knots was optimised by a 2-step optimisation procedure. The location of the knots was free to vary within the limits of time domain of the observed event data for the optimal placement to be achieved. Within each optimisation step, the location of the knots was

varied and the knot values fitted by maximum likelihood, attempting to find the global maximum likelihood set of knot location and values. The models produced were examined for physical plausibility (e.g., hazards positive at all times) and of the plausible models (in line with TSD 14 guidance in fit), the best fitting was selected, considerate of overfitting by Akaike Information Criterion. In both cases, these models had 2 internal knots.

The company would caution against using Royston-Parmar splines to model data with clear structural discontinuities, as this imposes conditions of smoothness on the hazard that are observed to be inconsistent with the data and can result in oscillation of the predictions and poor long-term performance due to the rapidly changing derivative of the hazard function. This is particularly true when a knot is placed near to such a discontinuity – this can occur in assessment driven data, which can result in a large number of events on the same study day, causing the model to prioritise instantaneous high hazard at that time at the cost of the physical plausibility of the hazard function around this point. The "Gelber" semi-parametric piecewise approach (referred to in TSD21 as a modification of the "Liverpool approach") does not impose this smoothness upon the model, and so pieces may begin immediately after a rapid change in hazard.

Further, spline fits provide a good fit to observed data, due to placement of knots to optimise the fit, but there is limited consideration or rationale for the extrapolation. As an example, knot placement does not take into account underlying biological mechanisms or potential subgroups within the data, both of which could be informing changing hazard profiles over time. Further, use of multiple knots provides improved fits but minimises available data to inform long-term extrapolations, resulting in potentially inappropriate predictions. As can be seen in Figure 38 and Figure 39, the provided spline models do not have an improved fit over the semi-parametric approach. Some models may even be considered inappropriate, due to the poor fit to the available data.

Specific to this analysis, the splines were fitted using *flexsurvspline*, a function defined in the "R" package *flexsurvreg*, in an all-cause framework, but for compliance with TSD21 they have been implemented incorporating external data (lifetables) for plausibility in extrapolation. Given that these models were not fitted in a relative survival framework, double-counting of this component of event hazard is present, as demonstrated by the separation of the curves in in Figure 38 and Figure 39.

Outcomes from the economic model are presented in Table 42. It should be noted that incremental costs and incremental QALYs are not greatly impacted by switching to a spline extrapolation approach, resulting in limited impact on the ICER. All analyses remain below standard willingness-to-pay thresholds.

Table 42. Economic model outcomes applying spline extrapolation models

Comparators		Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
PFS	Trifluridine-tipiracil	■	■	£13,734
	FOLFOX	■	■	£15,223
	FOLFIRI	■	■	£15,313
	Irinotecan	■	■	£15,406
	Raltitrexed	■	■	£15,749
	BSC	■	■	£14,566
ToT	Trifluridine-tipiracil	■	■	£13,034
	FOLFOX	■	■	£14,492
	FOLFIRI	■	■	£14,584
	Irinotecan	■	■	£14,675
	Raltitrexed	■	■	£14,982
	BSC	■	■	£13,889
PFS ToT	Trifluridine-tipiracil	■	■	£13,401
	FOLFOX	■	■	£14,875
	FOLFIRI	■	■	£14,967
	Irinotecan	■	■	£15,059
	Raltitrexed	■	■	£15,385
	BSC	■	■	£14,244

ICER: incremental cost-effectiveness ratio; Inc: incremental; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time on treatment

Note: OS is also available in the model but not presented here as it was not part of the question; available upon request
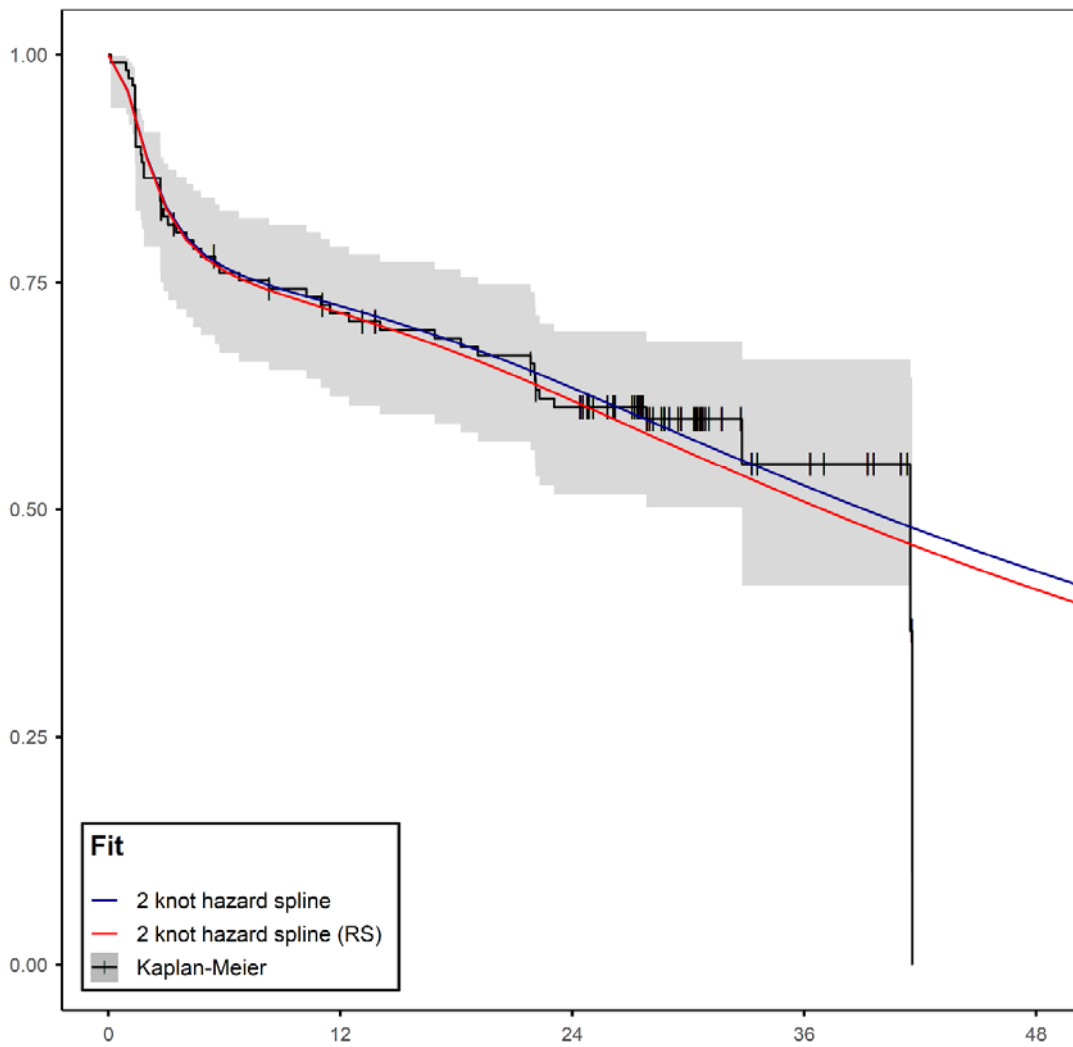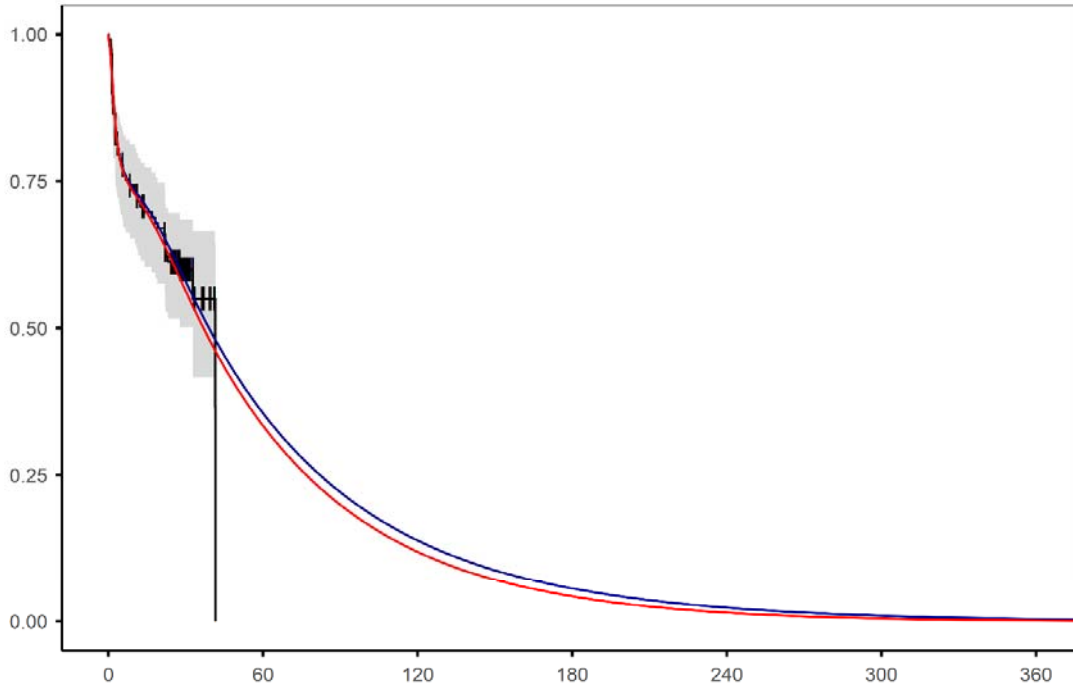
Figure 38. Spline model for progression-free survival per investigator for CheckMate 142 NIVO+IPI arm; RS: Relative survival
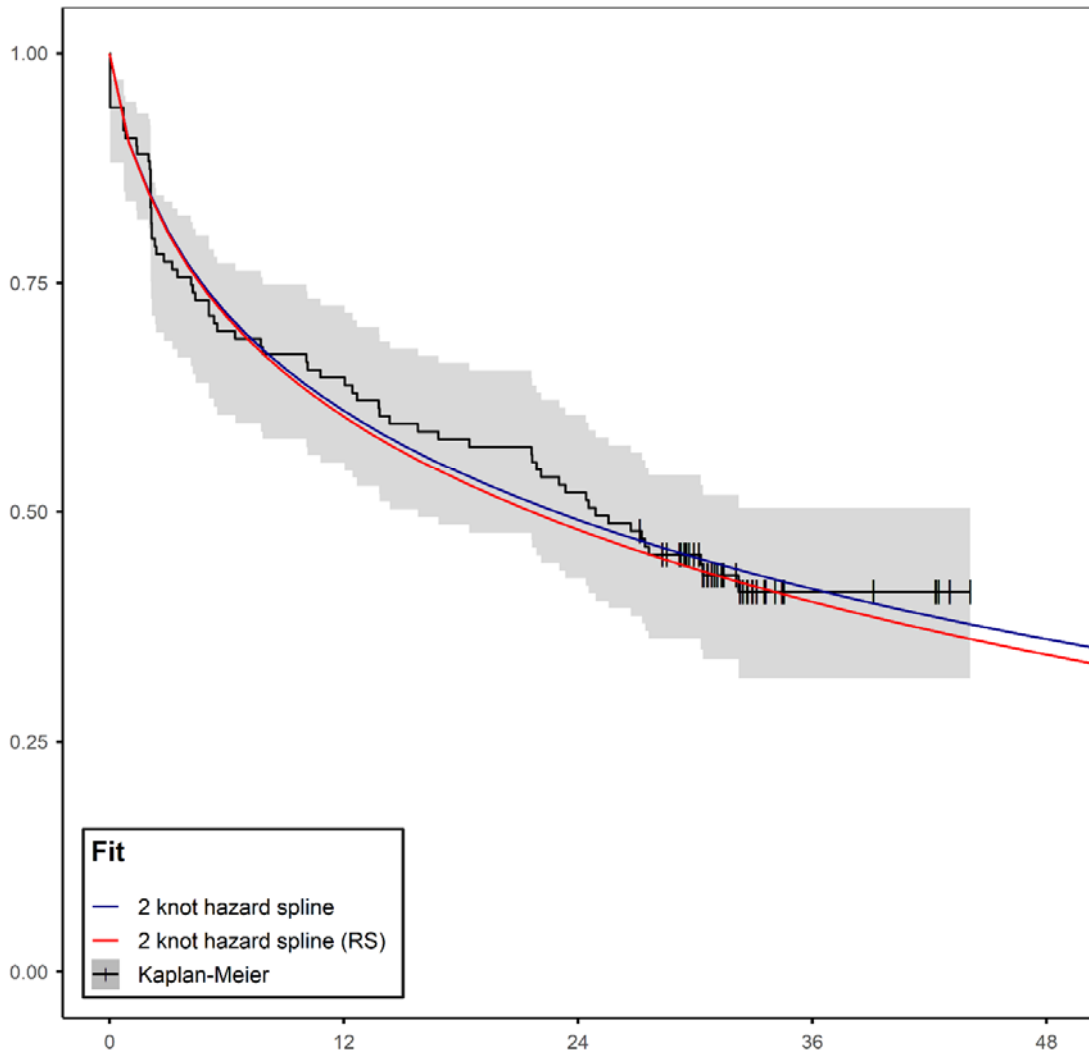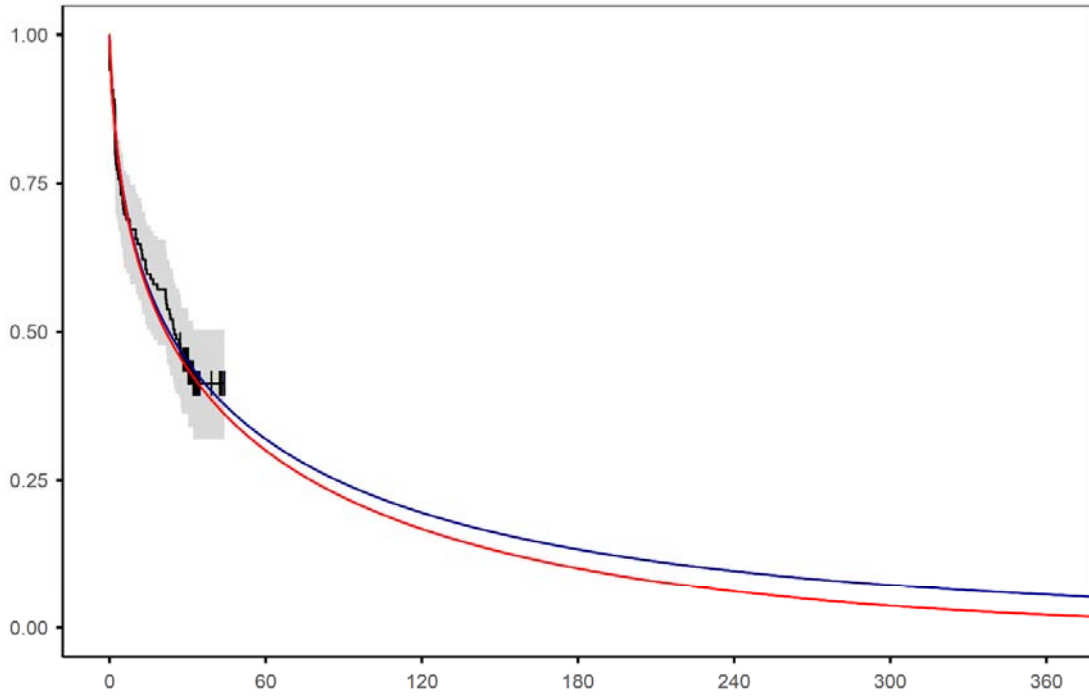
Figure 39. Spline model for time on treatment for CheckMate 142 NIVO+IPI arm; RS: Relative survival

B5. Priority question: According to NICE DSU TSD 21, "Sensitivity to time-points chosen should be explored." Additionally, based on the hazard profiles in Appendix M for PFS, TTD and OS, the high initial hazard approaches a lower, nearly constant value after 3 or 4 months. As a sensitivity analysis, please switch from KM data to a parametric extrapolation at 3 months. Please do this for PFS, TTD and OS, individually and collectively so that there are 4 sets of results.

The company disputes the statement "the high initial hazard approaches a lower, nearly constant value after 3 or 4 months". Figure 4 in Appendix M shows clearly that PFS hazard is at or near its peak at 3 months, depending on which independent hazard smoother is considered. The earliest point at which a "nearly constant" value could be considered would be near the point at which the estimators are at the value of the minimum value of the upper confidence bound of the bspline estimator – approximately 10 months for the bspline and kernel-smoothing estimators. Using visual smoothing only, it is also clear in panel (b) of figure 3 that curvature of the empirical cumulative hazard function continues to this point at a minimum.

In panel (b) of figure 14 of Appendix M, linearity of the empirical cumulative hazard function of OS is never satisfactorily approached, and this is represented by all smoothers (Figure 15) as a monotonically decreasing hazard from approximately 3 months.

Finally, the argument made for PFS can be repeated for ToT using figures 27 and 28. Nevertheless, in good faith, the sensitivity analysis requested was undertaken.

A scenario analysis was undertaken wherein the extrapolation was formed using Kaplan-Meier data to 2.99 months. When selecting cut points, it is best practice to avoid dates where assessments are scheduled, which reflect a short period where several events occur and hence may bias the extrapolation. Whilst the effect may not be large, it is considered to be more scientifically robust. This approach was applied within the survival analysis provided within the company submission and has continued to be used within this response. Patients in CheckMate 142 were evaluated every 6 weeks (±1 week) from first dose for the first 24 weeks and every 12 weeks (±1 week) thereafter. Based on this, the target assessment date at "12 weeks" would be 84 days, but this assessment can be made in the 7 days prior or post the target date (i.e., 77-91 days). Hence, the 2.99 month (i.e., 91 day) cut point was identified, so that all events occurring after 91.0 days will inform the survival extrapolation.

Figure 40, Figure 41 and Figure 42 show extrapolation models for time on treatment, PFS and OS, respectively. As can be observed, the fit to the data is not improved by using an earlier data cut. However, the base case parametric models remain the best approaches for fitting to the data (PFS: exponential; OS: log-logistic; time on treatment: log-logistic) and are provided for the economic analysis.

The impact of applying an alternative Kaplan-Meier cut point in the extrapolation is provided in Table 43. The ICER decreases versus all comparators when the updated time on treatment curve is used for NIVO+IPI. Similarly, the ICER decreases versus trifluridine-tipiracil when the updated NIVO+IPI PFS is applied. In all other scenarios, including OS for all comparators, the ICER is greater than the base case but remains below standard willingness-to-pay thresholds.

Table 43 Parametric extrapolation at 3 months

Comparators		Inc. QALY	Inc. Cost (£)	ICER (£/ QALY)
PFS	Trifluridine-tipiracil	5.819	£79,224	£13,616
	FOLFOX	5.565	£84,025	£15,099
	FOLFIRI	5.574	£84,675	£15,190
	Irinotecan	5.566	£85,063	£15,282
	Raltitrexed	5.302	£82,813	£15,619
	BSC	6.008	£86,822	£14,452
OS	Trifluridine-tipiracil	4.883	£74,307	£15,217
	FOLFOX	4.629	£79,108	£17,088
	FOLFIRI	4.639	£79,758	£17,193
	Irinotecan	4.631	£80,146	£17,308
	Raltitrexed	4.367	£77,896	£17,839
	BSC	5.072	£81,905	£16,148
ToT	Trifluridine-tipiracil	5.816	£76,910	£13,224
	FOLFOX	5.562	£81,711	£14,691
	FOLFIRI	5.572	£82,361	£14,782
	Irinotecan	5.563	£82,749	£14,87
	Raltitrexed	5.299	£80,499	£15,190
	BSC	6.005	£84,508	£14,073
PFS **OS** **ToT**	Trifluridine-tipiracil	4.880	£74,872	£15,342
	FOLFOX	4.627	£79,673	£17,221
	FOLFIRI	4.636	£80,323	£17,325
	Irinotecan	4.628	£80,711	£17,440
	Raltitrexed	4.364	£78,461	£17,980
	BSC	5.069	£82,470	£16,268
ICER: incremental cost-effectiveness ratio; Inc: incremental; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; ToT: time on treatment				

Cut at 2.99 months
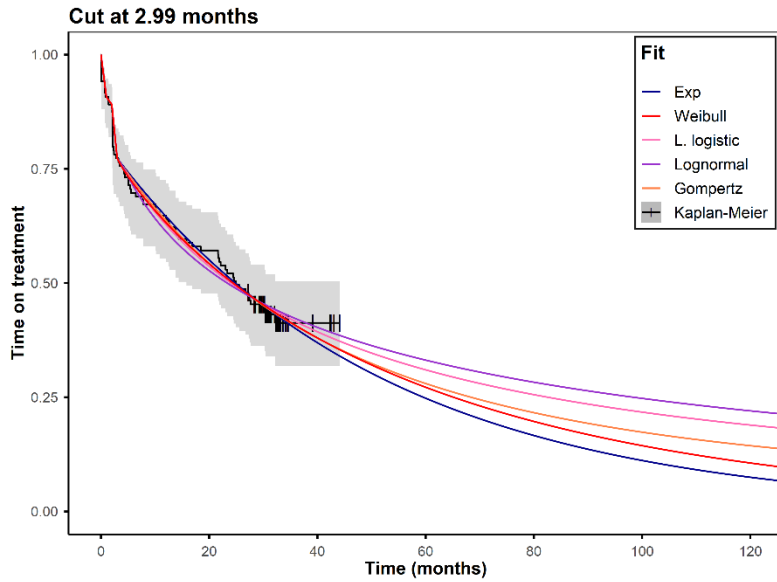
Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exp.	404.95	407.47	lambda: 0.0200	24.82 (18.07, 34.14)	41.35 (30.94, 56.05)
Weibull	406.33	411.37	shape: 0.8932; scale: 54.2519	24.40 (16.95, 34.61)	46.94 (31.56, 83.71)
Gompertz	406.74	411.78	shape: -0.0081; rate: 0.0223	24.32 (16.51, 35.01)	N/A (26.46, N/A)
L. logistic	407.04	412.08	shape: 1.0097; scale: 38.2978	24.03 (16.11, 34.99)	3071.22 (71.92, 5199.21)
Lognormal	408.25	413.29	mu: 3.7093; sigma: 1.8518	23.32 (15.16, 36.01)	177.91 (67.73, 749.83)

Figure 40. Time on treatment extrapolation using data cut at 2.99 months

Cut at 2.99 months
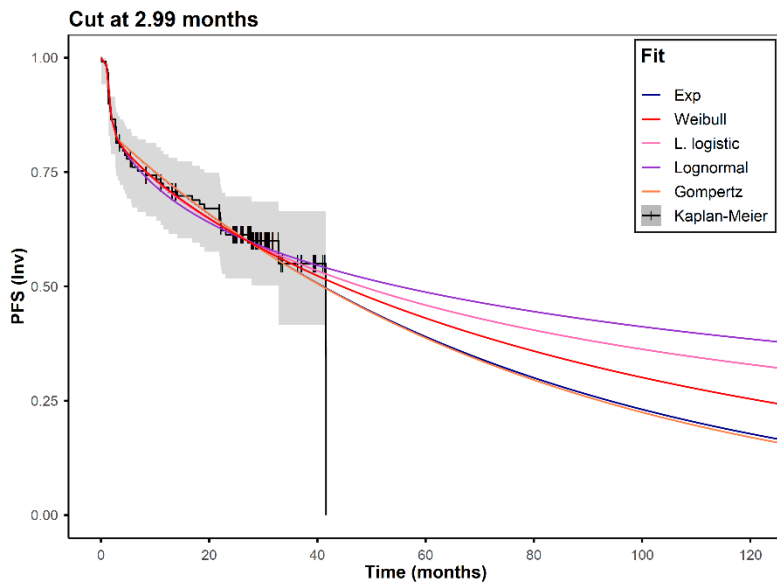
Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exp.	290.15	292.70	lambda: 0.0131	41.00 (28.92, 61.78)	65.59 (47.64, 97.75)
Weibull	291.02	296.12	shape: 0.8296; scale: 96.3876	44.54 (29.46, 81.34)	90.34 (45.97, 254.62)
Gompertz	292.15	297.26	shape: 0.0006; rate: 0.0130	40.87 (28.96, N/A)	63.35 (31.04, 72.77)
L. logistic	291.84	296.94	shape: 0.8866; scale: 74.2405	48.23 (29.96, 93.52)	N/A (96.59, N/A)
Lognormal	293.51	298.62	mu: 4.5801; sigma: 2.2850	55.10 (30.48, 123.20)	1093.83 (140.83, 16751.14)

Figure 41. PFS extrapolation using data cut at 2.99 months

Cut at 2.99 months
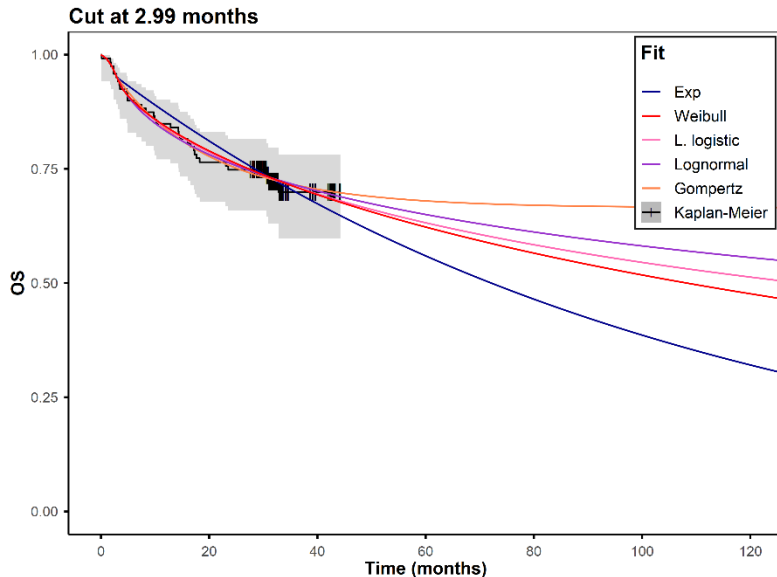
Fit Name	AIC	BIC	Parameters	Median (Months)	Mean (Months)
Exp.	308.71	311.44	lambda: 0.0093	72.10 (51.76, 109.01)	105.25 (74.65, 159.33)
Weibull	305.81	311.27	shape: 0.6823; scale: 201.7558	108.22 (61.26, 257.30)	251.62 (99.67, 1049.25)
Gompertz	305.82	311.27	shape: -0.0485; rate: 0.0173	N/A (79.72, N/A)	N/A (55.55, N/A)
L. logistic	305.59	311.05	shape: 0.7319; scale: 145.8844	129.16 (66.79, 354.30)	N/A (197.35, N/A)
Lognormal	305.64	311.09	mu: 5.3482; sigma: 2.7161	178.43 (76.84, 580.10)	7986.36 (491.52, 66498.71)

Figure 42. OS extrapolation using data cut at 2.99 months

B6. Priority question: Please explain how TTD curves have been calculated for the comparators in the economic model, this has been omitted from Document B.

a) **Please explain why medians rather means (except for BSC) have been used to inform these calculations (Table 29 of Document B).**

b) **Please clarify if 8 treatment cycles for FOLFIRI (Table 29 of Document B) is equal to 18.1 weeks of treatment, as reported in Van Cutsem et al. 2012.**

c) **Comparing the mean PFS for BSC in Table 26 of Document B (2.1 months) with the mean time on treatment in Table 29 (6.76 weeks) implies that BSC is stopped before progression. Please clarify why this would be the case.**

Time on treatment was used (defined as time from treatment initiation to last dose for patients who have discontinued treatment) rather than time to discontinuation (defined as time from treatment initiation to date of discontinuation). This is because date of discontinuation may overestimate time on treatment and will not reflect the patient experience of actual doses of therapy received.

Comparator time on treatment is based on published evidence, so available information is limited. Most frequently, the published literature reports mean or median number of cycles or time on treatment; no KM for time on treatment (or time to discontinuation) was identified. Mean data were applied where reported, but median data were converted to an exponential rate if required.

Once extracted, available information was standardised as far as possible. Studies reporting median cycles were standardised to median weeks and converted to an exponential rate. Studies reporting months, such as Van Cutsem et al. 2012, were used directly. Further information on how data were applied in the economic model is detailed in Table 44.

Table 44. Comparator time on treatment

	Median time on treatment	Exponential λ	Source
BSC*	6.76 weeks (not applied**)	NA	RECOURSE[48]
FOLFIRI	8 cycles (equivalent to 18.1 weeks as reported)	0.167	VELOUR[49]
FOLFOX	4.3 months	0.161	CONFIRM 2[10]
Irinotecan	4 cycles (equivalent to 12 weeks)	0.251	PICCOLO[50]
Raltitrexed	3 cycles (equivalent to 9 weeks)	0.335	Ugidos 2019[51]
Trifluridine-tipiracil*	12.65 weeks (mean value used to derive rate)	0.344	RECOURSE[48]
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin *mean time on treatment ** no BSC discontinuation is applied in the economic model Median values converted to exponential rates using formula: rate = ln(2)/median Mean values converted to exponential rates using formula: rate = 1/mean			

As noted in the company submission, patients may not discontinue from BSC. Hence, median time on treatment is not applied in the economic model; data is provided for completeness. However, the mean PFS and time on treatment information are correct as reported within the RECOURSE[27] study.

B7. Priority question: Rather than using the exponential distribution to model comparator PFS and OS please use the parametric distributions identified when estimating survival in the MAIC (Table 1 below). Please explain why these parametric distributions were not considered for the economic model.

Table 1. Summary of parametric distributions included in Table 30 of Appendix L

Comparator	Parametric distribution for OS	Parametric distribution for PFS
FOLFIRI	Generalised gamma	Lognormal
FOLFOX	Lognormal	Lognormal
BSC	Generalised gamma	Log logistic
Trifluridine-tipiracil	Lognormal	Generalised gamma
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin		

This analysis has been undertaken using the studies identified and adjustments made for question A11, in the hope that this would provide a more informative dataset for the ERG. Applied distributions across all scenarios are presented in Table 45. As can be seen in Table 45, using longer-tailed distributions has

resulted in a very slightly decreased ICER in the majority of cases, but at much less than 1%, the difference is not impactful.

Table 45. Scenario analysis: impact of parametric distributions to model comparator PFS and OS

Comparator	Study	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	ICER/QALY (exponential representation)
Trifluridine-tipiracil	RECOURSE EUR	■	■	£13,755	£13,783
	RESCOURSE USA	■	■	£13,415	£13,435
	TERRA	■	■	£13,105	£13,133
BSC	RECOURSE EUR	■	■	£14,424	£14,428
	RECOURSE USA	■	■	£14,163	£14,177
	LUME-Colon-1	■	■	£14,318	£14,339
	TERRA	■	■	£14,103	£14,101
FOLFOX	CONFIRM2	■	■	£14,778	£14,793
	NO16967	■	■	£14,660	£14,670
	CAPRI-GOIM	■	■	£15,487	£15,619
FOLFIRI	VELOUR	■	■	£15,813	£15,810
	RAISE	■	■	£15,373	£15,379
	NCT01479465	■	■	£18,436	£18,457
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Table 46: Distributions used for the comparator studies

Comparator	Study	OS distribution	PFS distribution
Trifluridine-tipiracil	RECOURSE EUR	Lognormal	Generalised gamma
	RESCOURSE USA	Lognormal	Generalised gamma
	TERRA	Log-logistic	Log-logistic
BSC	RECOURSE EUR	Generalised gamma	Log-logistic
	RECOURSE USA	Generalised gamma	Log-logistic
	LUME-Colon-1	Generalised gamma	Generalised gamma
	TERRA	Log-logistic	Log-logistic
FOLFOX	CONFIRM2	Lognormal	Lognormal
	NO16967	Generalised gamma	Weibull
	CAPRI-GOIM	Log-logistic	Log-logistic
FOLFIRI	VELOUR	Generalised gamma	Lognormal
	RAISE	Generalised gamma	Lognormal
	NCT01479465	Lognormal	Lognormal
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; OS: overall survival, PFS: progression free survival			

B8. Priority question: Please clarify why VELOUR was chosen as the base-case MAIC evidence source for FOLFIRI in the economic analysis.

a) Please provide a scenario analysis using RAISE as the evidence source.

Both studies were considered relevant to the decision problem, as both were large studies enrolling patients with similar patient characteristics to CheckMate 142. Tabernero 2015[9] (RAISE) required treatment with a specific first-line regimen (bevacizumab plus FOLFOX), which is not included in the UK treatment

pathway. Therefore, this study was deemed to be too specific to be included in the base case analysis, particularly in comparison with Van Cutsem 2012[8] (VELOUR). However, as outlined in response to Question B9 (Table 48), this analysis was included as a scenario in Section B.3.8.3.4 of the company submission.

B9. Priority question: Please include the scenarios listed in Section B.3.8.3.4 of Document B as executable options in the economic model.

All survival data for the scenarios described in Section B.3.8.3.4 of Document B are provided in the existing version of the model. Please refer to the model entitled "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking" and the relevant survival profile dropdown menus on the 'Model Control' worksheet. Alongside these clarifications, we have provided an additional user guide document to provide additional clarity with respect to the practical use of the model.

   a) **Please outline the data sources used to inform each of these scenarios.**

The base case economic analysis applies the best available evidence, which is the outcomes of base case MAIC analyses. However, scenario analyses were undertaken to reflect all available clinical efficacy estimates. The sources for each analysis are outlined in Table 48; NIVO+IPI remained as per the base case analysis inputs.

As can be seen, alternative efficacy inputs did not impact significantly on model outcomes. This is aligned to Table 52 from the company submission (reproduced below as Table 47), which demonstrates that the mean OS required to be cost-effective at a £50,000 per QALY willingness-to-pay threshold ranged from 34.2 months (versus BSC) to 49.1 months (versus raltitrexed). Given that OS is approximately ■ at five years of follow-up, it is extremely likely that the mean OS for NIVO+IPI reaches the threshold to be cost-effective at a £50,000/QALY threshold.

Table 47. Threshold analysis: NIVO+IPI mean OS and incremental QALYs

Technologies	Nivo+Ipi mean OS required to be CE at £50,000/QALY (months)	Incremental QALYs required to be CE at £50,000/QALY
Trifluridine-tipiracil	35.1	1.349
BSC	34.2	1.498
FOLFOX	43.2	1.443
FOLFIRI	43.3	1.457
Irinotecan	43.7	1.465
Raltitrexed	49.1	1.421
BSC: best supportive care; CE: cost-effective; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; OS: overall survival; QALY: quality-adjusted life year		

Table 48. Alternative measures of comparator efficacy

Scenario	Efficacy input vs model output	Outcome	Trifluridine-tipiracil	BSC	FOLFOX	FOLFIRI	Irinotecan	Raltitrexed
Base case	Source: MAIC base case analysis		RECOURSE EU population	RECOURSE EU population	CONFIRM2	VELOUR	PICCOLO	Ugidos
	Efficacy input	Mean PFS	4.2	2.1	4.5	6.3	6.7	8.6
		Mean OS	10.9	7.6	15.6	15.3	15.4	20.4
	Model output	Inc QALYs	█	█	█	█	█	█
		Inc Costs	█	█	█	█	█	█
		ICER	£13,366	£14,211	£14,839	£14,930	£15,022	£15,346
Alternative sources of comparator data	Source: MAIC scenario analysis		RECOURSE US population	RECOURSE US population	NA	RAISE	EPIC	NA
	Efficacy input	Mean PFS	3.7	1.9	NA	7.5	3.8	NA
		Mean OS	11.7	8.1	NA	17.2	13.3	NA
	Model output	Inc QALYs	█	█	NA	█	█	NA
		Inc Costs	█	█	NA	█	█	NA
		ICER	£13,418	£14,240	NA	£15,183	£14,673	NA
Unadjusted survival outcomes	Source: unadjusted comparison versus single studies		RECOURSE EU population	RECOURSE EU population	CONFIRM2	VELOUR	PICCOLO	Ugidos
	Efficacy input	Mean PFS	3.6	1.8	5.5	6.8	5.6	4
		Mean OS	10.4	7.2	17.3	15.7	14.6	8.5
	Model output	Inc QALYs	█	█	█	█	█	█
		Inc Costs	█	█	█	█	█	█
		ICER	£13,304	£14,177	£15,056	£14,993	£14,882	£13,937
Pooled survival outcomes (medians)	Source: Pooled median SLR outcomes (Table 14 of company submission)							
	Efficacy input	Median PFS	2.6	1.7	4.9	4.6	3.5	2.4
		Median OS	7.9	6.1	11.9	12.7	10.4	6.3
	Model output	Inc QALYs	█	█	█	█	█	█
		Inc Costs	█	█	█	█	█	█
		ICER	£13,393	£14,305	£15,117	£15,265	£14,906	£13,964

BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; IPI: ipilimumab; NR: not reported; OS: overall survival; PFS: progression-free survival

b) **On page 166 of Document B, please clarify what is meant by "An unadjusted analysis: based on combining comparator data from the SLR using standard meta-analysis techniques." According to the description on page 101, the unadjusted analysis should apply evidence from one study for each comparator (i.e. a naive comparison using CheckMate unadjusted vs the comparator unadjusted).**

The statement "An unadjusted analysis: based on combining comparator data from the SLR using standard meta-analysis techniques" is unclear and does not reflect the analysis provided. While undertaking the indirect comparison, comparator Kaplan-Meier data were digitised and extrapolated using standard parametric fits in order to obtain mean survival outcomes. These study-specific unadjusted survival outcomes from comparator studies were used in the economic model to provide a naïve comparison for one study for each comparator versus CheckMate 142 data. Output from this scenario analysis is provided in Table 16 (page 75) of the Company submission and reproduced above in Table 48.

Weighted average SLR outcomes for each comparator were also applied in the economic model, as outlined in Table 16 (page 75) of the Company submission and reproduced above in Table 48.

c) **Please provide the results of a naive comparison (CheckMate unadjusted vs Comparator unadjusted) if these are not already given in Table 62.**

Results of a naïve comparison (CheckMate 142 unadjusted versus comparator unadjusted) are shown in Table 62 (page169) in the company submission and reproduced above in Table 48.

B10. Please clarify if the time point (6.44 months) used to switch from KM data to a parametric extrapolation for TTD has only been chosen to match the time point used for PFS. Please comment on the appropriateness of this time point for TTD using Figure 27 of Appendix M.

Several factors influence the time point used to switch from Kaplan-Meier to a parametric extrapolation. This includes scheduled assessment periods, timing of events in the available data, time to response, underlying hazard profile and visual fit to the available data. As provided in the response to Question B5, Figure 40 and Figure 42 demonstrate that fit to available time on treatment and PFS data, respectively, is noticeably poorer at earlier time

points and provides implausible survival extrapolation. Hence, later time points for this switch are more appropriate for both time on treatment and PFS.

Due to the change in assessment scheduling after the fourth assessment, there is a structural change in both the PFS and time on treatment survival functions, becoming less obviously stepped and dependent upon assessment windows, more suitable for representation with a continuous model. To maximise the data available to inform the shape of this model, a time was chosen after the final assessment time within the regular 6-weekly schedule, but not so near that there would be an event "desert" as few patients would be attending for reassessment. 3 weeks (i.e., half of the previous cycle length) was chosen as appropriate.

All of these considerations applied equally for PFS and time on treatment, and the same conclusions were drawn.

With reference to Figure 27 (smoothed hazard function estimates of time on treatment), only the Royston-Parmar spline is capable of searching for and representing sharp hazard discontinuities, by placing adjacent knots. The last time it does this is at approximately 3 months, and beyond this time all estimators approach the same form – that of generally decreasing relative hazard. Given this, the process generating the hazard appears consistent from around this point, and a model was sought that was capable of demonstrating this hazard profile whilst preserving the features of the early trial. It is feasible that a point between 3 and 6 months could have provided a good fit statistically, but would not represent well the trial data which has clear reason for being non-continuous to 6 months.

The above was considered, as well as that consistency of approach is considered best practice when considering the time point of switching from Kaplan-Meier to extrapolation, as similar mechanisms underpin all three time to event data sets (PFS, OS and time on treatment), particularly PFS and time on treatment, which for many events have a directly causal relationship.

B11. Please clarify if the time point (6.44 months) used to switch from KM data to a parametric extrapolation for OS has only been chosen to match the time

point used for PFS. Please comment on the appropriateness of this time point for OS using Figures 14 and 15 of Appendix M.

None of the hazard functions demonstrated in Figure 15 can be adequately described by a standard parametric model, therefore more flexible methods were required, a variety of which were explored in depth in Appendix M. For the reasons given therein, a piecewise model was selected as an appropriate, conservative model that was well supported by available trial data, consideration of survival outcomes observed in other indications, and clinical opinion. Therefore, choice of time at which to initiate the long-term process which determines extrapolation was required. A large number of potential cut points was explored, with later cut points providing better fit to the tail of the data, but at the expense of confidence in the parameters of the model due to the lower number of events to fit to. Given that hazards were not obviously constant relative to lifetable in the tail, it was acknowledged that at least two parameters would require fitting, with the extrapolation likely to be very sensitive to the curvature of the excess hazard function in the tail, as the absolute value was already expected to be low in the observed period. Some consideration was given to the PFS and time on treatment models was given at this point. These models were forced to after the fourth assessment by discontinuity of the empirical cumulative hazard function, and even at this earliest reasonable time the uncertainty in the parameters of the extrapolative portion was large. Given that there were even fewer events in the tail of the OS curve to inform extrapolation, this point was therefore considered the latest at which the extrapolative model could be fitted without undue uncertainty about the shape of the model, but visually, fit also improved with later cut times, and therefore it was considered for base case. It was also at approximately this point that there was a sharp change in gradient of log cumulative hazard against log time versus the comparators (Figure 16), implying a change among the population around this time.

The company acknowledges that there is considerable uncertainty around the extrapolation of overall survival, and for this reason chose a model which was supported by the available data and clinical opinion, but was nevertheless expected to be conservative, as borne out by the later data cut-off of CheckMate 142 (page 2).

Alternative methods to model survival

B12. Priority question: To address the ERG's concerns in question A13, please provide results using the minimum number of assumptions to estimate the comparative treatment effect for NIVO+IPI and the comparators: provide

pairwise results using the adjusted Checkmate 142 data and unadjusted comparator trial data from the MAIC. Please use the parametric distributions summarised in Table 30 of Appendix L to extrapolate comparator PFS and OS in the economic model.

Analyses derived in response to Question A11 were assessed, requiring additional distributions compared to Table 30 of Appendix L; all distributions are provided in Table 49.

Outcomes from the scenario analyses where adjusted NIVO+IPI Kaplan-Meier is compared against unadjusted comparator outcomes are provided in Table 50. As can be seen, this has a larger impact on the ICER than alternative efficacy sources or alternative covariate sets. However, all analyses remain below standard willingness-to-pay thresholds. Further, this analysis should be viewed with caution, as this does not reflect comparator outcomes in an MSI-H/dMMR mCRC population as CheckMate 142 data has been adjusted to reflect the overall population sampled in the comparator studies. Hence, the base case analysis remains the most appropriate source of evidence to inform cost-effectiveness analyses.

Table 49. Scenario analysis: comparator parametric distributions

Comparator	Study	OS		PFS	
		Extrapolation	Mean outcome	Extrapolation	Mean outcome
Trifluridine-tipiracil	RECOURSE EUR	Lognormal	10.4	Generalised gamma	3.7
	RESCOURSE USA	Lognormal	11.7	Generalised gamma	3.6
	TERRA	Log-logistic	11.6	Generalised gamma	4.0
BSC	RECOURSE EUR	Generalised gamma	7.2	Log-logistic	1.8
	RECOURSE USA	Generalised gamma	8.1	Log-logistic	1.9
	LUNECOLON 1	Generalised gamma	10.2	Generalised gamma	1.9
	TERRA	Lognormal	8.7	Log-logistic	2.0
FOLFOX	CONFIRM2	Lognormal	17.3	Lognormal	5.5
	NO16967	Generalised gamma	14.0	Weibull	5.4
	CAPRIGOIM	Log-logistic	21.2	Log-logistic	6.7
FOLFIRI	VELOUR	Generalised gamma	15.7	Lognormal	6.8
	RAISE	Generalised gamma	16.2	Lognormal	6.6
	NCT01479465	Lognormal	21.0	Lognormal	8.2
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; OS: overall survival; PFS: progression-free survival					

Table 50. Scenario analysis: impact of alternative MAIC assumptions

Comparator	Study	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Trifluridine-tipiracil	RECOURSE EUR	███	██	£17,827
	RESCOURSE USA	███	██	£14,418
	TERRA	███	██	£11,160
BSC	RECOURSE EUR	███	██	£18,980
	RECOURSE USA	███	██	£13,739
	LUNECOLON 1	███	██	£14,988
	TERRA	███	██	£11,369
FOLFOX	CONFIRM2	███	██	£14,009
	NO16967	███	██	£15,024
	CAPRIGOIM	███	██	£16,748
FOLFIRI	VELOUR	███	██	£21,253
	RAISE	███	██	£18,045
	NCT01479465	███	██	£28,968
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year				

B13. Priority question: The ERG considers the OS data from Checkmate 142 to be highly immature. To reduce the uncertainty around the cost-effectiveness estimates please provide a scenario analysis assuming post-progression survival (PPS) is the same between the intervention and comparator (i.e. the mortality rate post-progression is the same regardless of treatment received). Please provide results using unadjusted Checkmate 142 data (base case analysis) and adjusted Checkmate 142 data (question B12).

As CheckMate 142 median OS has yet to be reached, it is acknowledged that this data cannot be considered fully mature. However, as data presented in the company submission provide median follow-up of ██ months, this indicates the significant OS benefit in comparison with other therapies. All identified RCTs report median OS less than two years for relevant comparators, while CheckMate 142 outcomes remain at approximately ██ at five years in the updated database lock presented in this clarifications response. In this context, survival data is sufficiently mature to conclude that outcomes are significantly improved versus comparators.

Available CheckMate 142 data documents the post-progression survival benefit; median post-progression survival ████████, as outlined in Figure 43, compared with data from comparator RCTs, where the most optimistic median OS estimate (i.e., pre- and post-progression survival) is 16.3 months. Hence, it is not appropriate to assume equivalent post-progression survival.
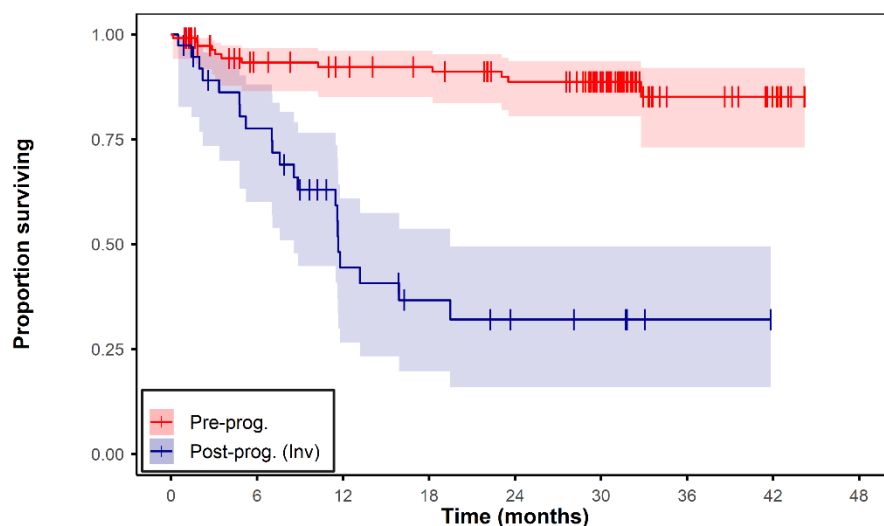
NAR (Cumulative Events)

Pre-prog.	119 (0)	90 (7)	85 (8)	82 (8)	73 (11)	58 (11)	15 (12)	9 (12)	0 (12)
Post-prog. (Inv)	38 (0)	27 (8)	12 (18)	8 (20)	5 (21)	4 (21)	1 (21)	0 (21)	0 (21)

Figure 43. CheckMate 142 pre-progression versus post-progression survival outcomes

In order to address the issue of data maturity, the company submission base case analysis is provided wherein the modelled time horizon is reduced to five years and ten years. The updated database lock provides observed data to beyond five years and strongly supports the continued benefit of NIVO+IPI, above the model predictions. Hence, this scenario analysis is subject to reduced uncertainty associated with immature data. As the model is supported by observed data to this timepoint, including any PPS, reducing the time horizon addresses the ERG concerns without assessing PPS explicitly.

As can be seen in Table 51, reducing the time horizon to five years reduced accrual of QALYs versus the base case resulting in higher ICERs. However, ICERs remained below a £50,000/QALY willingness-to-pay threshold.

Table 51. Scenario analysis: impact of reduced time horizon

	Ten-year time horizon			Five-year time horizon		
	Incremental costs	**Incremental QALYs**	**ICER (£/QALY)**	**Incremental costs**	**Incremental QALYs**	**ICER (£/QALY)**
Trifluridine-tipiracil	■	■	£19,862	■	■	£32,927
BSC	■	■	£20,916	■	■	£33,574
FOLFOX	■	■	£22,934	■	■	£40,315
FOLFIRI	■	■	£23,069	■	■	£40,494
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; IPI: ipilimumab; NR: not reported; OS: overall survival; PFS: progression-free survival						

B14. If the company believes there is a PPS benefit for NIVO+IPI, please consider a state transition model where PPS data is extrapolated and explicitly modelled, and OS is determined by the summation of the time spent in PFS and PPS. If PPS is not recorded in the comparator trials, consider estimating PPS assuming PPS=OS-PFS.

Constructing a state transition model has inherent limitations, including:

- As outlined in Figure 43, there are very few pre-progression death events during CheckMate 142, so that extrapolation of the data may produce spurious results and hence may reduce plausibility, particularly for MAIC outcomes.

- Post-progression survival outcomes are not available from comparator studies, which most commonly report PFS. As PFS definitions include deaths as PFS events, use of this data to inform a state transition model will result in double counting, biasing against comparators and increasing uncertainty.

- Post-progression survival is not equivalent to the difference between OS and PFS as by definition a proper survival random variable requires the modelled population to be at risk (conditional upon survival) at all times from 0, whereas no patients are at risk in the post-progression state at time 0. The defined measure is the expected cohort time in the post-progression state in a PSM, and any hazard of state exit estimated from this requires very strong assumptions for extrapolation, as there is no appeal to the characteristics of distributions of proper random variables to define the unobserved domain and it is not independent of the PFS function. Time to death from progression, distributed by the post-progression survival function, is the correct proper random variable to consider, but this distribution function is challenging to

identify without post-progression survival data and if dependent upon progression time is unidentifiable in all but degenerate cases.

Based on this rationale, as well as the time required to build a state transition model and analyse available comparator data, a state transition model is not considered appropriate. However, the simplified assessment provided in B13 should provide additional information on the impact of any uncertainty in PPS extrapolation.

All-cause mortality (ACM)

B15. Priority question: From the company's submission, the ERG considers that the company has estimated a survival curve for ACM and applied this multiplicatively to disease-specific mortality from Checkmate 142 in the NIVO+IPI treatment arm. According to NICE DSU TSD 21, submissions considering excess mortality need to isolate the cause-specific mortality by partitioning the ACM into that due to other causes and the excess mortality caused by the disease of interest. TSD 21 also states that assumptions are still necessary about the long-term extrapolations of the disease-specific and other-cause mortality; that is, the long-term hazard functions for each cause of interest must still be defined to extrapolate appropriately. In light of this, can the company please:

   a) **Describe or re-assess how their method to include ACM aligns with the advice in TSD 21.**

   b) **Justify why ACM is applied from week 29 and week 2,609 for the intervention and comparators, respectively.**

CheckMate 142 OS from treatment initiation to week 29 is based on direct KM data (equivalent to cut point in semi-parametric extrapolation). Hence, it is assumed that any impact of ACM is captured in this data.

After this point, it is assumed that observed events are insufficient to capture the very long-term increasing risk of ACM in an aging population. Hence, ACM is applied multiplicatively (hazards are added) in the economic model from week 29 to week 2,609. For the comparator, the means informing the relative mean value from the ITC are both inclusive of general population ACM. This relative mean is then multiplied by a reference mean from a model of the CheckMate 142 NIVO+IPI population including ACM, therefore the adjusted

mean is inclusive of both components. In order to prevent the model applying ACM to the modelled comparator survival curve, the mechanism to prevent double-counting in the piecewise models is used, setting ACM multiplication to start at the final model cycle.

B16. Please include an executable option in the model where OS is capped by ACM and PFS is capped by OS.

The model combines mortality as estimated from the trial Kaplan-Meier data, in the NIVO+IPI base using a semi-parametric log-logistic function. To account for increasing general population mortality, general population mortality is also applied from the point at which the parametric function is utilised (cycle 29). The two survival functions are combined multiplicatively, and this is already applied in the current version of the model. This may be turned on and off in the 'Life Tables' worksheet.

With regards to PFS, the model already contains a catch for any scenarios in which the PFS curve is greater than the OS curve – see e.g., Cell "J11" on the "Outcomes Trace" sheet. As PFS and OS are multiplied by the same ACM, it is sufficient to set the disease specific survival portion of the PFS model to the minimum of the calculated value and that of OS.

A scenario was conducted to assess the impact of applying disease-specific mortality up until the point that the hazard of ACM exceeds the OS, at which point ACM survival is applied. As can be seen in Table 52, the cost-effectiveness outcomes are improved, with increased life expectancy observed in the NIVO+IPI arm.

Table 52. Scenario analysis: OS capped by ACM

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	███	██	██	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	██	██	██	**£12,016**
BSC	£9,379	0.626	0.441	██	██	██	**£12,780**
FOLFOX	£12,176	1.258	0.884	██	██	██	**£13,219**
FOLFIRI	£11,527	1.231	0.874	██	██	██	**£13,299**
Irinotecan	£11,139	1.240	0.883	██	██	██	**£13,375**

Health-related quality of life

B17. As advised by the NICE DSU TSD 12, please compare the population and methods in Checkmate 142 with CORRECT.

CheckMate 142 was a non-comparative study, while CORRECT was a randomised, placebo-controlled, phase 3 study. Further, eligibility in CORRECT specified that patients had to have received locally and currently approved standard therapies, including as many of the following as licensed: a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab; and cetuximab or panitumumab for patients who had KRAS wild-type tumours. As a result, patients in CORRECT are more treatment-experienced, as outlined in Table 53. Patients in CheckMate 142 were less likely to have KRAS mutations but were more likely to have ECOG status 1 and BRAF mutations.

Table 53. Comparison of baseline characteristics from CORRECT and CheckMate 142

		Regorafenib		Placebo		NIVO+IPI	
		N	%	N	%	N	%
Number of patients		505		255		119	
Age	Median, years [IQR]	61	(54·0–67·0)	61	(54·0–68·0)	58	NR
Sex	Men	311	62%	153	60%	70	58.8%
Race	White	392	78%	201	79%	110	92.4%
	Black	6	1%	8	3%	2	1.7%
	Asian	76	15%	35	14%	3	2.5%
ECOG performance status	0	265	52%	146	57%	54	45.4%
	1	240	48%	109	43%	65	54.6%
KRAS mutation	No	205	41%	94	37%	NR	NR
	Yes	273	54%	157	62%	44	37.0%
	Unknown	27	5%	4	2%	NR	NR
BRAF mutation	No	322/336	96%	163/166	98%	NR	NR
	Yes	14/336	4%	3/166	2%	44	25.2%
Number of previous systemic anticancer therapies (on or after diagnosis of metastatic disease)	1–2	135	27%	63	25%	71	59.6%
	3	125	25%	72	28%	48	36.1%
	≥4	245	49%	120	47%	NR	NR
Previous anti-VEGF treatment	Bevacizumab	505	100%	255	100%	68	57.1%

B18. Please provide utility values (including the mean, 95% confidence interval and number of responses) for the following situations in Checkmate 142:

    a) PFS, on and off treatment

    b) PFS, off treatment

    c) PFS, on treatment

    d) PD, on and off treatment

    e) PD, on treatment

Table 54. Utility values by health state observed in Checkmate 142

Health state	Observations	Utility (95% confidence interval)
PFS	1759	0.839 (0.821,0.857)
PFS, off treatment	108	0.872 (0.814,0.930)
PFS, on treatment	1651	0.837 (0.818,0.856)
PD	208	0.850 (0.804,0.896)
PD, on treatment	66	0.728 (0.603,0.852)

B19. As a scenario analysis, please add AE-related utility decrements to the existing scenario which NIVO+IPI utility values as per comparators (Scenario B.3.8.3.7 of Document B).

Adverse event utility data for colorectal cancer patients is scarce, as demonstrated in recent technology appraisals TA439[52], TA405[53] and TA240[54], where multiple different values have been used and utility values specific to colorectal cancer patients have not been available. Identification of adverse event utility data for the subgroup of patients relevant to this submission, namely adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy, has subsequently not been possible.

However, to demonstrate the potential impact of including additional utility decrements associated with the modelled adverse events, we have provided an analysis assessing the impact of increasing adverse event disutility. Disutility values for all adverse events were varied between 0 and 0.5 and the impact on the incremental QALYs and the ICER for each treatment comparison were recorded. As suggested, the basis of this analysis was Scenario

B.3.8.3.7 of Document B. Figure 44 demonstrates this impact. Notably, utilising even the largest disutility value of 0.5 did not impact cost-effectiveness conclusions.
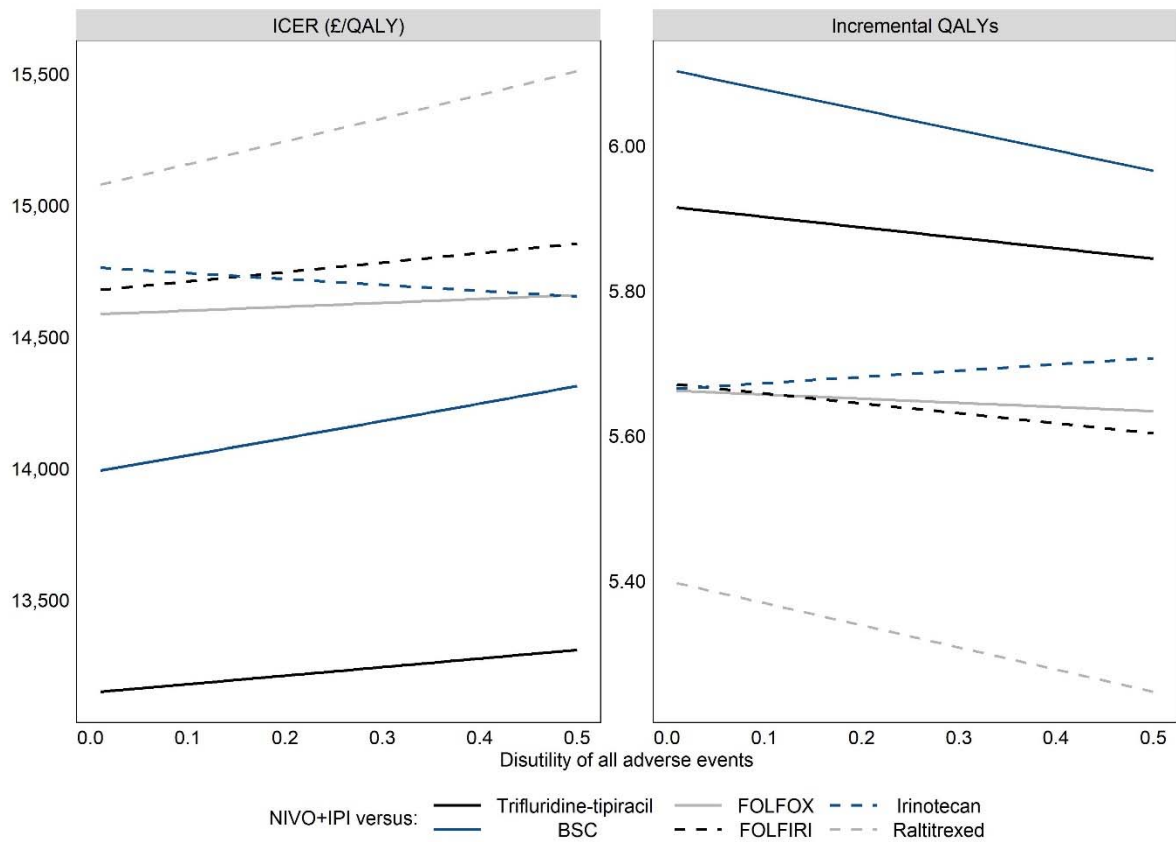
Figure 44. Impact of adverse event disutility on incremental QALY and ICER outcomes

B20. Please consider whether the utility values derived from CORRECT are representative of people with high MSI or DNA MMR deficiency, who may have a lower quality of life than the broader population with metastatic CRC.

Clinical validation suggests that patients with MSI-H/dMMR mCRC may have worse prognosis than the overall population, which may be related to lower quality of life. Hence, use of the CORRECT population to inform MSI-H/dMMR utilities may be considered optimistic, favouring the comparator population. However, this is the best available evidence to inform MSI-H/dMMR utilities.

Resources and costs

B21. Priority question: Please provide a scenario analysis where the treatment stopping rule for NIVO+IPI is removed and NIVO+IPI cannot continue beyond progression.

Conventional anti-cancer therapies typically aim to reduce the tumour burden through disruption of cell proliferation or induction of apoptosis. By contrast, due to their novel mechanism of action immuno-oncology therapies demonstrate a varied pattern of response, including the appearance of larger tumours due to the increased immune cell activity in the tumour environment. This pattern of response is a well-recognised challenge associated with immuno-oncology therapies, and can result in dissociated responses, delayed responses and pseudo-progressions, where patients who ultimately achieve a positive clinical outcome may have tumours that appear to have enlarged when assessed in the early stages of treatment.

With this in mind, the cost-effectiveness model was designed such that a proportion of patients may receive treatment with NIVO+IPI after progression, in line with observations from CheckMate 142 and consistent with expected real-world usage. As such, we do not believe the requested scenario is an appropriate representation of the use of NIVO+IPI.

However, as requested, we have undertaken this scenario analysis. The scenario may be replicated using the existing model version entitled ""Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking" and using the stopping rule parameters provided (see the 'Stopping rules' tab in the 'Treatment Arm Profile: Second Line' menu on the 'Model Control' worksheet). Time on treatment input data remained as in the base case. Results of this analysis can be seen in the table below.

Table 55. Scenario analysis: impact of no stopping rule for NIVO+IPI and no post-progression treatment with NIVO+IPI

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■	■	■	**£22,008**
BSC	£9,379	0.626	0.441	■	■	■	**£22,564**
FOLFOX	£12,176	1.258	0.884	■	■	■	**£23,818**
FOLFIRI	£11,527	1.231	0.874	■	■	■	**£23,892**
Irinotecan	£11,139	1.240	0.883	■	■	■	**£23,994**
Raltitrexed	£13,389	1.616	1.147	■	■	■	**£24,740**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

B22. Priority question: Please provide a scenario analysis where patients only begin 3rd line therapy upon progression (and not upon progression or discontinuation)

The model structure has not been constructed to formally enable such an analysis. However, to address the ERGs concerns we have endeavoured to provide an ad-hoc adaptation of the model to undertake this analysis. To implement this scenario, time on treatment was capped by PFS where necessary to ensure that only patients in the progression-free health state were receiving 2nd line therapy. Subsequently, a proportion of patients discontinued 2nd line treatment and remained in the progression-free health state. Only patients that moved to the progression health state were assumed to start 3rd line therapy. Stopping rules remained as in the base case. Results of the analysis may be found in Table 56 and do not differ significantly to those of the base case analysis.

Table 56. Scenario analysis: impact of limiting the start of 3rd line therapy to patients that have progressed (and not those that have discontinued 2nd line and remain in the progression-free health state)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	■■	■■	■■	-	-	-	-
Trifluridine-tipiracil	£16,786	0.887	0.630	■■	■■	■■	**£13,432**
FOLFOX	£11,019	1.258	0.884	■■	■■	■■	**£15,081**
FOLFIRI	£10,566	1.231	0.874	■■	■■	■■	**£15,136**
Irinotecan	£9,959	1.240	0.883	■■	■■	■■	**£15,268**
Raltitrexed	£12,025	1.616	1.147	■■	■■	■■	**£15,639**
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

B23. Priority question: Please justify why pre-progression health state costs are assumed to be the same for NIVO+IPI and each comparator.

 a) **The SmPC for NIVO+IPI states that patients should be monitored for cardiac and pulmonary adverse reactions continuously and that patients should be monitored at least up to 5 months after the last dose. Please add these monitoring costs to the economic analysis.**

In line with the request, it is assumed that all patients receive monitoring for cardiac and pulmonary adverse reactions, equivalent to one GP visit, one echocardiogram and one lab test every four weeks. Table 57 provides the resource costs used to monitor for cardiac and

pulmonary adverse reactions via a blood count test, an echocardiogram and a GP visit. This cost is applied up to treatment discontinuation, at which point five months of monitoring costs are applied.

Table 57. Resource costs used to monitor cardiac and pulmonary adverse reactions

Resource	Unit cost (£)	Source
Full blood count	£2.79	National cost collection: directly accessed pathology services, currency code DAPS05[55]
Echocardiogram	£256.61	National cost collection: Total HRG's, currency code EY50Z[55]
GP visit	£167.24	National cost collection: weighted average of consultant and non-consultant-led general medicine, service code 300, currency codes WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C, WF02D[55]

Table 58 presents the cost-effectiveness results for this scenario and as can be seen, this had minimal impact on the ICERs.

Table 58. Scenario analysis: impact of clinician consultation costs

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£17,028	0.887	0.630	■	■	■	£13,496
BSC	£9,511	0.626	0.441	■	■	■	£14,336
FOLFOX	£12,288	1.258	0.884	■	■	■	£14,974
FOLFIRI	£11,636	1.231	0.874	■	■	■	£15,065
Irinotecan	£11,212	1.240	0.883	■	■	■	£15,157
Raltitrexed	£13,441	1.616	1.147	■	■	■	£15,487
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

b) **The ERG's clinical advisors stated that they would expect patients to have 1 visit with a consultant oncologist before starting NIVO+IPI, 1 visit while on NIVO+IPI and then quarterly visits while on NIVO as a monotherapy. Please provide a scenario analysis which includes these estimates.**

The cost for a clinician consultation was sourced from the National Cost Collection[55] using a weighted average of consultant-led clinical consultation (codes WF01A, WF01B, WF01C, WF01D, WF02A, WF02B, WF02C and WF02D; service code 370), yielding a cost of £197.70.

Table 59 presents the cost-effectiveness results for this scenario and as can be seen, this had minimal impact on the ICERs.

Table 59. Scenario analysis: impact of clinician consultation costs

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■	■	■	£13,599
BSC	£9,379	0.626	0.441	■	■	■	£14,436
FOLFOX	£12,176	1.258	0.884	■	■	■	£15,082
FOLFIRI	£11,527	1.231	0.874	■	■	■	£15,172
Irinotecan	£11,139	1.240	0.883	■	■	■	£15,265
Raltitrexed	£13,389	1.616	1.147	■	■	■	£15,600
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

B24. Please provide a scenario analysis which includes the following resources for all treatments in addition to the health state resources outlined in Table 44 of Document B:

a) **During PFS:**

    i.   **1 CT scan at 12 weeks, 6 months and then once per year thereafter**

    ii.   **1 CT scan at treatment cessation**

b) **During PD:**

    i.   **1 consultant oncologist outpatient visit every 6 months**

    ii.   **1 CT scan once per year to five years**

The cost for a CT scan was sourced from the National Cost Collection[55] using a weighted average of computerised tomography scans (codes RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z and RD27Z), yielding a cost of £97.15. The cost for a clinician consultation was calculated as described in Question B23.

For the scenarios where costs are included in the progressed disease state, a simplifying assumption was made where costs were averaged out into a weekly cost in order to be applied in line with the model weekly cycle length.

Table 60 presents the cost-effectiveness results for all four scenarios and as can be seen, none of the scenarios had a large impact on the ICERs in comparison to the base case.

Table 60. Scenario analysis: impact of clinician consultation costs

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
a) i 1 CT scan at 12 weeks, 6 months and then once per year thereafter							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£17,028	0.887	0.630	■	■	■	£13,371
BSC	£9,511	0.626	0.441	■	■	■	£14,201
FOLFOX	£12,288	1.258	0.884	■	■	■	£14,832
FOLFIRI	£11,636	1.231	0.874	■	■	■	£14,294
Irinotecan	£11,212	1.240	0.883	■	■	■	£15,023
Raltitrexed	£13,441	1.616	1.147	■	■	■	£15,350
a) ii CT scan at treatment cessation							
NIVO+IPI	■	■	■	-	-	-	**-**
Trifluridine-tipiracil	£17,048	0.887	0.630	■	■	■	£13,361
BSC	£9,379	0.626	0.441	■	■	■	£14,217
FOLFOX	£12,234	1.258	0.884	■	■	■	£14,835
FOLFIRI	£11,584	1.231	0.874	■	■	■	£14,926
Irinotecan	£11,209	1.240	0.883	■	■	■	£15,016
Raltitrexed	£13,470	1.616	1.147	■	■	■	£15,337
b) i 1 consultant outpatient visit every 6 months							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£17,177	0.887	0.630	■	■	■	£13,643
BSC	£9,545	0.626	0.441	■	■	■	£14,484
FOLFOX	£12,505	1.258	0.884	■	■	■	£15,104
FOLFIRI	£11,790	1.231	0.874	■	■	■	£15,207
Irinotecan	£11,395	1.240	0.883	■	■	■	£15,300
Raltitrexed	£13,728	1.616	1.147	■	■	■	£15,622
b) ii 1 CT scan once per year every five years							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£17,102	0.887	0.630	■	■	■	£13,539
BSC	£9,482	0.626	0.441	■	■	■	£14,381
FOLFOX	£12,381	1.258	0.884	■	■	■	£15,004
FOLFIRI	£11,691	1.231	0.874	■	■	■	£15,102
Irinotecan	£11,298	1.240	0.883	■	■	■	£15,195
Raltitrexed	£13,600	1.616	1.147	■	■	■	£15,518
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

B25. The time horizon for the model is listed as 2,609 weeks, however the costs are only set to run for a maximum of 2,088 weeks. Please explain this discrepancy.

As suggested the last week in which 2nd line treatment costs are applied is week 2,088. Given that all patients have discontinued in both arms prior to week 2,088 this does not impact results. However, for consistency we have now updated these input parameters so that 2nd line treatment costs are applied up to week 2,609. Please see attached model.

B26. On page 98 of Document B it states, "it is assumed that patients may not discontinue this final line of therapy." With this in mind, please explain why the same one-off subsequent treatment cost is applied to all treatment arms when these treatment arms have different survival times.

a) **Please provide a scenario analysis where subsequent treatment costs (BSC) reflect the time in the PD health state.**

In the base case analysis, a one-off cost for subsequent treatment is applied to all patients in the first cycle after discontinuation. In order to facilitate this analysis, weekly costs were instead applied in order to reflect the time patients are in post-progression. Patients receiving trifluridine-tipiracil had a mean OS of 9.1 months and mean PFS of 3.7 months, resulting in a mean time of 5.4 months (23.5 weeks) in post-progression, as reported in TA405[53]. This mean time in post-progression was used to scale the one-off subsequent treatment cost into an average weekly cost. Subsequent treatment costs of £1,528.00 for trifluridine-tipiracil were sourced from TA405[53] and inflated to a present day cost of £1,643.49 (inflation factor of 1.061). This was then scaled to a weekly cost of £69.99, which was applied to all patients in post-progression.

As can be seen in Table 61, the impact of this scenario analysis had minimal impact on cost-effectiveness outcomes.

Table 61. Scenario analysis: impact of subsequent treatment costs

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	███	███	███	-	-	-	-
Trifluridine-tipiracil	£18,141	0.887	0.630	███	███	███	£13,309
BSC	£9,379	0.626	0.441	███	███	███	£14,348
FOLFOX	£13,925	1.258	0.884	███	███	███	£14,673
FOLFIRI	£13,229	1.231	0.874	███	███	███	£14,773
Irinotecan	£13,255	1.240	0.883	███	███	███	£14,790
Raltitrexed	£16,990	1.616	1.147	███	███	███	£14,822
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years							

B27. Please confirm why trifluridine-tipiracil followed by BSC was not modelled after irinotecan or raltitrexed in the subsequent therapy scenario analysis (Table 28 of Document B).

Clinical expert opinion confirmed that both single agent irinotecan and raltitrexed are rarely used in clinical practice (<5% patients), and mainly in patients where other treatments are contraindicated. Hence, it is unlikely that trifluridine-tipiracil would be provided to patients progressing on irinotecan or raltitrexed. However, it should be noted that these comparators have limited relevance to the UK decision problem.

B28. Please provide a scenario in which 10% wastage is assumed for oral treatments (e.g. trifluridine tipiracil), to align with the committee's preference in ID1598 (Section 3.31). In line with the committee's preference, the scenario should assume that all patients waste 10% of tablets, rather than 10% of patients waste tablets.

It is anticipated that the clinical reality of tablet wastage results in patients missing doses rather than consuming the complete course of tablets and wasting additional tablets on top of this. Resultantly, it is unlikely that the cost of treatment would be affected, but rather that the efficacy of the treatment may differ in the real-world, with real-world efficacy likely lower than that of a clinical trial due to missed doses. However, it is not possible to estimate such an impact.

To address the review groups concerns we have provided two scenarios assessing the impact of additional trifluridine/tipiracil tablet usage to account for potential wastage. Table 41 in document B describes the dosing and cost calculations for trifluridine/tipiracil with an expectancy that 60 20mg/8.19mg tablets are required each cycle (28 days), with tablets

available in packs of 20. The first scenario assumes that to achieve complete dosing, an additional 6 tablets (10% wastage) are required each cycle and that the remainder of the 20-tablet pack is not wasted. The second scenario takes the same approach but assumes an additional cost associated with the entire 20-tablet pack.

Resultantly, the additional cost per cycle for trifluridine/tipiracil in Scenario 1 is £200 (the cost of 6 tablets) giving a total cost per cycle of £2,395.44, whilst the additional cost per cycle for trifluridine/tipiracil in Scenario 2 is £666.66 (the cost of 20 tablets) giving a total cost per cycle of £2,862.10.

Results of the analysis are presented in Table 62.

Table 62. Scenario analysis: impact of trifluridine/tipiracil wastage

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Scenario 1: trifluridine/tipiracil cyclic cost of £2,395.44							
NIVO+IPI	■■■	■■■	■■■	-	-	-	-
Trifluridine-tipiracil	£17,682	0.887	0.630	■■■	■■■	■■■	**£13,246**
Scenario 2: trifluridine/tipiracil cyclic cost of £2,862.11							
NIVO+IPI	■■■	■■■	■■■	-	-	-	-
Trifluridine-tipiracil	£19,326	0.887	0.630	■■■	■■■	■■■	**£12,963**

Section C: Textual clarification and additional points

C1. Priority question: The ERG has some major issues with the usability and transparency of the model:

a) **The ERG has identified several discrepancies between the model and Document B. Due to time constraints the ERG has not been able to note down every discrepancy and validate every input or scenario, a few are listed in Table 2 below. Please perform a thorough model validation and make any necessary corrections. If no errors are found, please provide a detailed breakdown of how to set up the model for each comparison.**

Table 63. Discrepancies between the model and submission

Description	Value in model	Location in model	Value in Document B
Results for trifluridine-tipiracil	£123	Results!J17	£126
	£16,978	Results!E10	£16,981
	£77,781	Results!E11	£77,777
	£13,367	Results!H11	£13,366
Scenario 2, assumed to represent a comparison between nivo+ipi and BSC. Please note that the ERG can replicate the company's results by changing the profiles to BSC: Model Control!L23:38	£14,209	Scenario Analysis Results!R11	£14,211
	£85,373	Scenario Analysis Results!N11	£85,379
Scenario 3, assumed to represent a comparison between nivo+ipi and FOLFOX. Please note that the ERG can replicate the company's results by changing the profiles to FOLFOX: Model Control!L23:38	£14,873	Scenario Analysis Results!R12	£14,839
	£82,773	Scenario Analysis Results!N12	£82,582
Scenario B.3.8.3.7 alternative utilities selected in Model Control!F51. Comparison with trifluridine-tipiracil	£13,644	Results!H11, due to time constraints only discrepancies in the ICERs are reported here	£13,148
Scenario B.3.8.3.7 alternative utilities selected in Model Control!F51. Comparison with FOLFOX	£15,161		£14,585
Scenario B.3.8.3.7 alternative utilities selected in Model Control!F51. Comparison with FOLFIRI	£15,254		£14,675

Scenario B.3.8.3.7 alternative utilities selected in Model Control!F51. Comparison with BSC	£14,496		£13,985
Post progression cost	£46.77	Profile pop up	£203.38 monthly (£46.93 equivalent weekly)
BSC administration cost	£49.33	Profile pop up	£0
Trifluridine-tipiracil cost	£2,000	Profile pop up	2 doses per day at £100 per dose

In response to the ERGs comments and requests for further validation of the model, as suggested, we have undertaken further testing of the model and its input parameters, alongside evaluating the specific scenarios highlighted by the ERG in Table 63. Importantly, we identify no errors with the model itself and highlight below, in an adapted version of the table above (Table 64) explanations for the inconsistency between the ERGs model results and Document B.

Further, for each of the scenario analyses and the base case analysis we have provided below brief guidance as to how to implement such analyses within the model.

1. **Base case analysis**: For each base case scenario the relevant PFS, OS and time on treatment profile should be selected from the respective dropdown menus on the 'Model Control' worksheet. Users should ensure that the 'Include discontinuation?' setting is set to 'Yes' and that the 'Discontinuation' setting is set to 'Time on Treatment'. The 'Treatment arm utilities as on treatment/off treatment?' setting should also be set to 'Yes'.

   An exception to this is the analysis of NIVO+IPI versus BSC, where in the 'Control Arm' the 'Include discontinuation?' setting should be set to 'No'.

   Note: When the 'Include discontinuation?' setting is changed the 'Discontinuation setting' defaults to 'Discontinuation'; users should ensure this is set to 'Time on Treatment' for all base case analyses.

2. **Alternative extrapolation of NIVO+IPI survival (B.3.8.3.2):** For each of these scenario analyses only the relevant PFS, OS or time on treatment profile for the 'Treatment Arm' should be changed using the relevant dropdown menu. All relevant survival profiles are pre-populated within the model. No other changes to model settings are required.

3. ***Subsequent therapy:*** As outlined previously, trifluridine-tipiracil may be a more relevant comparator in patients who are more heavily pre-treated. Hence, patients

failing NIVO+IPI, FOLFOX or FOLFIRI may receive trifluridine-tipiracil before progressing to the subsequent therapy observed in TA405[53]. To evaluate this scenario, users should change the comparison so that either FOLFOX or FOLFIRI are evaluated (as in the base case). Subsequently, users should click the 'Control Arm Profile: Third Line' button and using the dropdown menu select the treatment profile entitled: 'Scenario B.3.8.3.3 Trifluridine/Tipiracil' and then click 'Load'. The same process should then be followed for the 'Treatment Arm'.

4. **Alternative sources of comparator efficacy:** For each of these scenarios, the PFS and OS profiles of the 'Control Arm' should be changed simultaneously to represent the relevant alternative sources of comparator efficacy that are pre-loaded within the model. All other settings should remain as in the base case.

5. **Impact of applying BICR-assessed PFS:** For each of these scenarios, the PFS profile of the 'Treatment Arm' should be changed to the profile entitled 'Section B.3.8.3.5: BICR Assessed PFS'. All other settings should remain as in the base case.

6. **Impact of removing stopping rules:** To remove stopping rules from an analysis, users should click the 'Treatment Arm Profile: Second Line' button and navigate to the tab entitled 'Stopping rules'. On this tab, to remove stopping rules, users should change the Boolean 'Use stopping rule' options to 'False'. Alternatively, users may load the profile entitled 'Scenario B.3.8.3.6: NIVO+IPI (No Stopping Rule)', where these inputs are already specified. The same process can be undertaken for the 'Control Arm' if necessary, and other stopping rule scenarios may be investigated.

7. **Impact of alternative utilities:** Given the uncertainty in application of treatment-specific utilities, values from the published literature were assessed in scenario analysis, wherein NIVO+IPI utility values were assumed as per comparators and applied by progression status, as opposed to treatment status, as in the base case. To evaluate this scenario, users should click the 'Utility Profile' button and load the profile entitled 'Scenario B.3.8.3.7: Alternative Utilities'. Next, to ensure that the new utility values are applied by progression status, as opposed to treatment status, users should change the option entitled 'Treatment arm utilities as on treatment/off treatment?' to 'No'.

8. **Impact of inclusion of testing for MSI test cost:** To assess the impact of including costs for MSI testing, users should click the 'Treatment Arm Profile: Second Line' button and load the profile entitled 'Scenario B.3.8.3.8: NIVO+IPI (MSI-H Test Cost)'. This profile utilises different costs as specified in the 'Treatment costs' tab. All other settings should remain as in the base case.

9. **Remission in a proportion of patients:** To assess the impact of remission, users should click the 'Treatment Arm Profile: Second Line' button and load the profile entitled 'Scenario B.3.8.3.9: NIVO+IPI (Remission State)'. This profile utilises different remission options as specified in the 'Remission' tab. To change these settings manually, users should navigate to the 'Remission' tab and change the Boolean 'Include remission state?' option to true. Subsequent settings allow users to specify the proportion of patients in remission, and the time point at which this proportion is assessed. From the time point specified, the proportion of patients that are deemed to be in remission incur general population mortality and utility estimates

Table 64: Company explanations for ERG proposed discrepancies between the model and submission

Description	Value in model	Location in model	Value in Document B	Location in Document B	Explanation of discrepancy
Results for trifluridine-tipiracil	£123	Results!J17	£126	Table 50	These results were updated in a resubmitted version of Document B and were acknowledged as a typographical error on part of the company.
	£16,978	Results!E10	£16,981		
	£77,781	Results!E11	£77,777		
	£13,367	Results!H11	£13,366		
Scenario 2, assumed to represent a comparison between nivo+ipi and BSC. Please note that the ERG can replicate the company's results by changing the profiles to BSC: Model Control!L23:38	£14,209	Scenario Analysis Results!R11	£14,211	Table 50	The values presented in Document B are correct and align to model results. Further, the model provided to the ERG was setup such that the base case analyses could be run individually. The model was not setup such that 'Scenario Analysis' worksheets would produce these results. Therefore, we believe the ERG has set the model incorrectly for this scenario. Subsequently, we have endeavoured to provide further guidance on the setup of the model for different scenario analyses, and have provided a version of the model which is setup with appropriate profiles for use of the 'Scenario Analysis' worksheets.
	£85,373	Scenario Analysis Results!N11	£85,379		
Scenario 3, assumed to	£14,873	Scenario Analysis	£14,839	Table 50	

represent a comparison between nivo+ipi and FOLFOX. Please note that the ERG can replicate the company's results by changing the profiles to FOLFOX: Model Control!L23:38		Results!R12			The values presented in Document B are correct and align to model results. Further, the model provided to the ERG was setup such that the base case analyses could be run individually. The model was not setup such that 'Scenario Analysis' worksheets would produce these results. Therefore, we believe the ERG has set the model incorrectly for this scenario. Subsequently, we have endeavoured to provide further guidance on the setup of the model for different scenario analyses, and have provided a version of the model which is setup with appropriate profiles for use of the 'Scenario Analysis' worksheets.
	£82,773	Scenario Analysis Results!N12	£82,582		
Scenario B.3.8.3.7 alternative utilities selected in Model Control!F51. Comparison with trifluridine-tipiracil	£13,644	Results!H11, due to time constraints only discrepancies in the ICERs are reported here	£13,148	Table 66	The values presented in Document B are correct and align to model results. Therefore, we believe the ERG has set the model incorrectly for this scenario. Subsequently, we have endeavoured to provide further guidance on the setup of the model for different scenario analyses.
Scenario B.3.8.3.7 alternative utilities selected in Model Control!F51. Comparison with FOLFOX	£15,161		£14,585		
Scenario B.3.8.3.7 alternative utilities selected in Model Control!F51. Comparison with FOLFIRI	£15,254		£14,675		
Scenario B.3.8.3.7 alternative utilities selected in Model Control!F51. Comparison with BSC	£14,496		£13,985		
Post progression cost	£46.77	Profile pop up	£203.38 monthly (£46.93 equivalent weekly)	Table 44	The total monthly value presented in Document B is correct and aligns to the weekly model input parameter. To generate the weekly value the monthly value is divided by the number of weeks in a month calculated with the following formula: (365.25/12)/7 Our calculations are based upon a 12-month year with

					365.25 days per year, and 7 days per week. The values given in brackets in Table 44 are standard error values.
BSC administration cost	£49.33	Profile pop up	£0	Table 41	Table 44 of Document B outlines the health state costs, with a footnote saying only patients receiving BSC receive this cost, for a medical oncologist outpatient consultation. This cost is £197.70 (when rounded to 2dp) which is a 28-day cost, so when changing to a weekly cost, divided by 4, results in £49.33.
Trifluridine-tipiracil cost	£2,000	Profile pop up	2 doses per day at £100 per dose	Table 41	We believe this to be correct, in both the model and in Document B. Indeed 2 doses per day at £100 per dose are applied. However, patients receive those doses for 10 days total in each cycle resulting in a cyclic cost of £2,000.

b) **To increase transparency and enable the ERG to perform additional scenarios in the model please:**

   i. **Add more descriptive labels to parameters in the data library and profile pop-ups rather than having them as component 1, component 2, etc.**

This has been undertaken in the provided models.

   ii. **Replace the hard-coded values in the economic model with calculations that employ the inputs reported in the submission (e.g. using parameters for dose and patient weight/body surface area to calculate treatment acquisition costs)**

Dose calculations were undertaken outside the model, as detailed in Company submission Section B.3.5.1.3. This was considered to be appropriate as the key cost driver was anticipated to be the cost of NIVO+IPI. As the standard error of baseline patient weight was 1.65kg in CheckMate 142 (mean: 73.7kg), there is negligible impact when sampling from a normal distribution, it is expected that only 0.008% of probabilistic analysis runs would utilise a different NIVO+IPI cost to that used in the base case.

    iii.   **Enable alternative scenarios to be run on top of the base case analysis. The ERG has found that loaded alternative assumptions in profile pop-ups are reverted back to base case assumptions when the model is run, for example, removing stopping rules in the NIVO+IPI arm (Document B Section B.3.8.3.6) and including remission in a proportion of patients (Document B Section B.3.8.3.9).**

This functionality is currently incorporated within the model. Alongside these clarifications, we have provided an additional user guide document to provide additional clarity with respect to the practical use of the model.

C2. Priority question: Please replace the hard-coded survival curves in the economic model with survival curves that are calculated within the economic model.

Fully parametric survival curves are currently incorporated within the economic model and can be selected or modified for alternative analyses. However, it is not feasible to provide semi-parametric survival curves in the economic model in a manner that will enable PSAs to be undertaken correctly without providing patient-level data in the model. The format of the semi-parametric models requires provision of Kaplan-Meier data to inform the initial part of the survival curve followed by a parametric model that could be informed by a functional form, using standard extrapolation parameters. However, under the best case where the covariance matrix was appropriately scaled, parametric sampling during the PSA would result in decorrelation between two pieces of the semi-parametric model, resulting in implausible results and if left at its default the covariance matrix would not reflect any uncertainty in the Kaplan-Meier portion of the model; instead, sampling is performed offline by bootstrapping from the patient-level data; the 95% confidence interval of the survival predictions from this bootstrap are provided and assumed distributed normally on the log cumulative hazard scale for the purpose of sampling within the economic model. Hence, the semi-parametric forms are provided in the data library, to facilitate assessment.

C3. Please add 10, 20, 30, 40 and 50-year predictions to Tables 24 and 25 of Document B.

Tables 24 and 25 of Document B provide direct comparison of observed survival and survival as predicted by the parametric and semi-parametric survival curves over the first 24 months. These comparisons are made using the survival functions directly, without adjustment for all-cause mortality.

Given the request for predictions at significantly later time points outside of the trial period, we have presented output directly from the cost-effectiveness model using each of the different survival curves, after incorporating the impact of all-cause mortality (as in the base case cost-effectiveness analysis). Where the cycle did not precisely align to the requested time point (for example, the 10-year time point lies in between cycle 521 and cycle 522 due to the weekly cycle length), the 'FORECAST' function in Excel was used to approximate the exact survival.

Predictions have been provided for those survival curves which were deemed appropriate for use in cost-effectiveness analyses. Those that did not represent an adequate fit to the underlying survival data are not presented, consistent with the submission and the provided model.

Table 65. Model predicted progression-free survival for NIVO+IPI (including ACM)

Time	Fully parametric	Semi-parametric					
	Generalised Gamma	Exponential	Generalised Gamma	Gompertz	Log-Logistic	Log-Normal	Weibull
6 months	79.1%	76.1%	76.1%	76.1%	76.1%	76.1%	76.1%
1 year	70.6%	71.5%	72.3%	72.8%	72.2%	71.6%	72.3%
2 years	61.9%	62.8%	63.3%	64.3%	63.2%	62.6%	63.2%
10 years	41.6%	21.8%	0.0%	0.0%	25.0%	33.1%	15.8%
20 years	29.4%	5.2%	0.0%	0.0%	10.9%	18.5%	1.9%
30 years	15.1%	0.8%	0.0%	0.0%	4.0%	7.9%	0.1%
40 years	2.5%	0.0%	0.0%	0.0%	0.5%	1.1%	0.0%
50 years	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

Table 66. Model predicted overall survival for NIVO+IPI (including ACM)

Time	Fully parametric				Semi-parametric					
	Generalised Gamma	Log-Logistic	Log-Normal	Weibull	Exponential	Generalised Gamma	Gompertz	Log-Logistic	Log-Normal	Weibull
6 months	91.3%	91.9%	91.5%	92.0%	89.9%	89.9%	89.9%	89.9%	89.9%	89.9%
1 year	85.5%	86.4%	85.8%	86.7%	86.0%	84.1%	84.0%	84.0%	83.5%	84.1%
2 years	78.1%	78.4%	78.2%	78.9%	78.5%	77.3%	76.6%	77.2%	77.0%	77.4%
10 years	53.3%	48.1%	51.8%	44.6%	37.1%	50.5%	64.7%	51.7%	56.5%	49.3%
20 years	36.3%	29.5%	34.2%	22.8%	13.1%	30.9%	53.5%	33.6%	40.3%	28.7%
30 years	17.9%	13.5%	16.5%	8.5%	3.1%	13.6%	30.1%	15.9%	20.5%	11.9%
40 years	2.8%	2.0%	2.5%	1.0%	0.2%	1.9%	5.2%	2.4%	3.3%	1.6%
50 years	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

C4. Please explain why the model schematic in the model (worksheet Model Overview) differs from the Document B (Figure 24).

Both model depictions are provided in Figure 45. The model includes three states: Pre-progression, post-progression and death. These states are stratified by treatment status in order to enable flexible treatment cost calculation. Hence, both model schematics are correct.
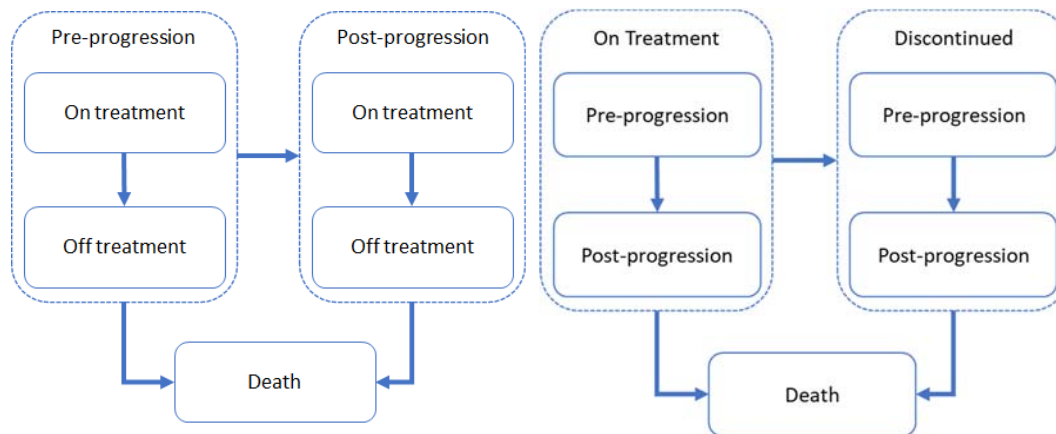
Figure 45. Comparison of economic model schematics

C5. According to the ERG's clinical experts, the mean age of patients with mCRC in UK clinical practice is 72 years. Please provide a scenario analysis using this mean age of patients in UK clinical practice.

The majority of patients in CheckMate 142 were <65 years of age (68%), in contrast to clinical practice where the majority of patients are predicted to be >65 years of age.[45, 56] However, this was not corroborated by UK clinical expert opinion, which confirmed that patients with dMMR/MSI-H mCRC tend to be younger in UK clinical practice. This is supported by a UK real-world evidence study, detailed in Section B.2.13.4.1. of Document B. Further, patients with Lynch syndrome typically develop cancers at a younger age, making the results more relevant to the UK. Despite this, as detailed in Section B.2.7 of Document B, NIVO+IPI is equally efficacious in older patients (ORR 60.5% vs 57.9% in patients <65 years and >65 years, respectively).[7]

Further, and importantly, model input parameters are calibrated to the baseline age used in the model, with results of the ITC analyses highly dependent on patients' age. Adjusting the age to a significantly higher value renders the statistical analysis utilised to generate model inputs redundant. Hence, outcomes of this scenario analysis should be considered with caution and with these significant limitations in mind.

Table 67. Scenario analysis: impact of alternative baseline age assumptions (baseline age = 72 years)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.567	■	■	■	**£19,723**
BSC	£9,379	0.626	0.397	■	■	■	**£20,813**
FOLFOX	£12,176	1.258	0.795	■	■	■	**£22,385**
FOLFIRI	£11,527	1.231	0.787	■	■	■	**£22,522**
Irinotecan	£11,139	1.240	0.795	■	■	■	**£22,682**
Raltitrexed	£13,389	1.616	1.032	■	■	■	**£23,643**

C6. Please vary patient weight in a one-way sensitivity analysis and probabilistic sensitivity analysis.

Weight impacts only the cost of NIVO+IPI and the associated cost calculations are detailed in Table 35 and Table 36 of Document B. As requested, we have undertaken a one-way sensitivity analysis in which we vary the average patient weight by ±20%. Updated cost estimates for NIVO+IPI in each scenario are provided in the table below (Table 68). Subsequently, results of the one-way sensitivity analysis may be found in Table 69.

With regards to incorporating weight into the PSA, given that the standard error of baseline patient weight was 1.65kg in CheckMate 142 (mean: 73.7kg), when sampling from a normal distribution, it is expected that only 0.008% of probabilistic analysis runs would utilise a different NIVO+IPI cost to that used in the base case. Given this negligible impact, a requirement to structurally alter the model to incorporate such analysis and the limited time in which responses need to be provided, we have not undertaken this adaptation, and instead, hope the demonstration of its negligible impact proves adequate.

Table 68. One-way sensitivity analysis weight calculations

Scenario	Dosing	Weight	Cost (excluding PAS)	Dosing per cycle	Total cost per cycle (£)[1]
Nivolumab					
Base case	3mg/kg by intravenous infusion over 30 mins every 3 weeks for 4 doses and then 240mg every 2 weeks thereafter	73.7kg	10mg/ml concentration for solution for infusion in vial, 4ml=£439.00; 10ml=£1,097.00; 24ml=£2,633.00	240mg	£2,633.00[2] £2,874.06[3]
Scenario 1: Weight -20%		58.96kg		200mg[2] 240mg[3]	£2,194.00[2] £2,874.06[3]
Scenario 2: Weight +20%		88.44kg		280mg[2] 240mg[3]	£3,072.00[2] £2,874.06[3]
Ipilimumab					
Base case		73.7kg		100 mg	

Scenario 1: Weight -20%	1mg/kg by intravenous infusion over 90 mins every 3 weeks for 4 doses	58.96kg	5mg/ml conc for soln for inf in vial, 10ml=£3,750.00; 40ml=£15,000.00		£7,870.68
Scenario 2: Weight +20%		88.44kg			

[1]Administration costs applied as normal
[2]per treatment cycle (applied every 3 weeks for 4 cycles)
[3]per treatment cycle (applied every 2 weeks from week 13)

Table 69. One-way sensitivity analysis: impact of alternative baseline weight assumptions

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Scenario 1: Weight -20% (58.96kg)							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■	■	■	**£13,197**
BSC	£9,379	0.626	0.441	■	■	■	**£14,046**
FOLFOX	£12,176	1.258	0.884	■	■	■	**£14,661**
FOLFIRI	£11,527	1.231	0.874	■	■	■	**£14,753**
Irinotecan	£11,139	1.240	0.883	■	■	■	**£14,845**
Raltitrexed	£13,389	1.616	1.147	■	■	■	**£15,159**
Scenario 2: Weight +20% (88.44kg)							
NIVO+IPI	■	■	■	-	-	-	-
Trifluridine-tipiracil	£16,978	0.887	0.630	■	■	■	**£13,537**
BSC	£9,379	0.626	0.441	■	■	■	**£14,375**
FOLFOX	£12,176	1.258	0.884	■	■	■	**£15,016**
FOLFIRI	£11,527	1.231	0.874	■	■	■	**£15,107**
Irinotecan	£11,139	1.240	0.883	■	■	■	**£15,200**
Raltitrexed	£13,389	1.616	1.147	■	■	■	**£15,532**

BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: : 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

C7. Please explain why the mean values for PFS and OS in Table 26 of Document B are not an exact match with the mean values obtained from the economic model (Table 50 of Document B).

The comparator mean PFS and OS values specified in Table 26 of Document B are based on MAIC outcomes but do not reflect the impact of ACM, which is applied as an additional source of mortality in the model. Hence the modelled OS outcomes vary slightly from the MAIC outcomes.

C8. Please clarify why a half-cycle correction was not applied in the economic model.

Half-cycle corrections are not required in economic models where the cycle length is short and where treatment costs are applied at specific intervals. The economic model has a weekly cycle length, which can be considered fairly short. Additionally, treatment costs are applied every two to three weeks, with the exception of trifluridine-tipiracil. Hence, a half-cycle correction is not required in the economic model.

C9. Please explain the "reference" values in tab Survival!H.

As outlined in response to Question A13, the MAIC outputs relative treatment effect as a difference between log mean survival outcomes for comparator and adjusted NIVO+IPI data. These values are applied to the unadjusted NIVO+IPI log mean survival outcomes. Hence, the reference values reflect the log mean unadjusted NIVO+IPI survival values onto which the difference in log means is applied to derive adjusted comparator survival outcomes.

C10. Please explain how "the timing of these discontinuations was assumed to impact on the incidence of AEs" in the economic model (page 111 of Document B).

Adverse events are applied as a one-off event in the initial cycle, as the majority of patients with Grade 3–4 events will either discontinue treatment or will have no further events. Hence, events applied as a cyclic rate will overestimate incidence when extrapolated over a long-term horizon. Hence, discontinuation, as observed from the clinical trial, was assumed to impact on the modelled AEs.

C11. In Figure 1 of Document B, please clarify why some NICE guidance has not been referenced. For example, aflibercept in combination with irinotecan and fluorouracil-based therapy is not recommended within its marketing authorisation for treating metastatic CRC that is resistant to or has progressed after an oxaliplatin-containing regimen (NICE TA307). It appears that Figure 1 is not limited to positive NICE recommendations, as references to bevacizumab not being recommended have been included.

According to the NICE treatment pathway, biological therapy as second-line treatment for metastatic disease has been removed from the schematic. Figure 1 in the company submission represents the most recent NICE treatment pathway schematic and the following negative recommendations are therefore not listed:

- Aflibercept in combination with irinotecan and fluorouracil-based therapy is not recommended

- Cetuximab monotherapy or combination chemotherapy is not recommended

- Bevacizumab monotherapy or combination chemotherapy is not recommended

- Panitumumab monotherapy is not recommended

Panitumumab in combination with chemotherapy was terminated as no evidence submission was received

C12. Please provide further detail as to when preliminary results will be available for CheckMate 8HW.

Preliminary results are currently expected in ███

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7.	Bristol-Myers Squibb. Study CA209142: Ad hoc efficacy report. 2019.

8.	Van Cutsem E, Joulain F, Hoff PM, Mitchell E, Ruff P, Lakomý R, et al. Aflibercept Plus FOLFIRI vs. Placebo Plus FOLFIRI in Second-Line Metastatic Colorectal Cancer: a Post Hoc Analysis of Survival from the Phase III VELOUR Study Subsequent to Exclusion of Patients who had Recurrence During or Within 6 Months of Completing Adjuvant Oxaliplatin-Based Therapy. Target Oncol. 2016;11(3):383-400.

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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]

Clarification questions

November 2020

File name	Version	Contains confidential information	Date

Additional information request from ERG

A dependent relationship in the economic model appears to be missing. This relates to questions B3, B4, B5, B15 and C2, and in general anywhere where there is a change in the parametric distribution used to extrapolate survival data from CheckMate 142.

Can the company link the mean survival times from alternative extrapolations with the mean survival times for NIVO+IPI in the MAIC so that the extrapolation method is consistent?

Currently, these steps in the economic model are independent because the MAIC can only be informed by a semi-parametric distribution including 6.44 months of KM data.

There is a lack of clinical evidence describing standard chemotherapies as a treatment for MSI-H/dMMR mCRC, particularly in patients who have received prior therapies. Hence, the provided MAIC analysis aims to provide a measure of comparative efficacy in the population of interest (MSI-H/dMMR mCRC, represented by CheckMate 142). The baseline characteristics for CheckMate 142 patients receiving NIVO+IPI are adjusted to match those for comparator studies (previously treated mCRC regardless of MSI-H/dMMR status) by applying a weight to each patient. These weights are then applied to derive clinical outcomes, which can be used to inform a relative treatment effect which is then transported to the patient population of interest (MSI-H/dMMR mCRC). This transportation of the relative treatment effect is essential in order to ensure that the absolute treatment values reflect the efficacy of therapies in the population of interest.

Alternative approaches to conducting a MAIC in this population are summarised in Table 1.

Table 1. Alternative approaches to MAIC implementation

Approach	Limitation
Conduct MAIC using mean survival outcomes, where mean survival outcome for comparator is the primary outcome	Mean survival outcomes are not observed in any study where Kaplan-Meier is not closed, so that extrapolation is required prior to undertaking the MAIC.
Conduct MAIC using Kaplan-Meier data and provide extrapolations based on adjusted NIVO+IPI Kaplan-Meier in each comparator study population	This would reflect the efficacy of NIVO+IPI in previously treated mCRC patients regardless of MSI-H/dMMR status (which is not the relevant population for decision making).
Conduct MAIC using median survival outcomes, where median survival outcome for comparator is the primary outcome	Median survival outcomes are not observed in CheckMate 142, requiring extrapolation, resulting in challenges equivalent to modelling to the mean survival outcomes, but without reflecting the long-term hazard progression.
Conduct MAIC using survival outcomes at specific time points, where mean survival at time point for comparator is the primary outcome	Analysis of a single time point would bias against NIVO+IPI, as it would not reflect the observed decrease in hazards over time. Multiple discrete timepoints could be assessed, resulting in a low-resolution approximation of a function. However, this would have no basis for extrapolation and hence would not be informative for economic modelling
Conduct MAIC using restricted mean survival outcomes, where mean survival at time point for comparator is the primary outcome	This analysis would use observed data, so would be subject to less uncertainty. However, as the data is not sufficiently mature, this would not be useful to inform economic modelling.

As can be seen, all approaches have associated challenges, so that the approach applied in the company submission is the most appropriate and informative, while requiring least assumptions. If it were appropriate to assess NIVO+IPI efficacy in the comparator study population, it would be feasible to provide an economic model reflecting extrapolations fitted to adjusted Kaplan-Meier for NIVO+IPI for each comparator study. However, as the efficacy needs to be assessed in an MSI-H/dMMR mCRC population, the model input is required to be the relative treatment effect, derived from the MAIC. Because of this, it is not feasible to provide an economic model where changing the survival extrapolation for NIVO+IPI impacts the comparator outcomes automatically, as this would need to be calculated outside the in advance and provided within the model.

The current economic model includes MAIC output (relative mean survival measures), based on using the base case survival extrapolation for NIVO+IPI (semi-parametric applying Kaplan-Meier to 6.44 months; OS uses log-logistic extrapolation and PFS uses exponential extrapolation). In order to provide an economic model relevant to the ERG's request, MAIC analyses have been provided using other NIVO+IPI extrapolations. As all fully parametric extrapolations provide poor fits to the data, these are not provided. Additionally, semi-parametric extrapolations with alternative cut points were not used, as these provided poor fits to the data or outputs that may be considered implausibly optimistic. Hence, MAIC analyses were undertaken using all extrapolations for NIVO+IPI OS and PFS for the 6.44-month semi-parametric fits. This includes all scenarios provided in response to A11, detailed in Table 22 and Table 23, and applying the same method to covariate set derivation. The relative treatment effects (applied as the difference in log mean survival) were applied in the economic model, so that selection of the NIVO+IPI parametric extrapolation changes the comparator mean survival outcomes, linking the economic model survival input with the MAIC survival inputs and hence MAIC outputs.

The MAIC outputs are detailed in Table 2 to Table 13. Although the relative treatment effect was highly variable, when these were applied to the NIVO+IPI mean survival the resultant absolute outcomes were broadly comparable to that provided previously in A11. Absolute outcomes were more highly variable were effective sample size was lower, such as comparisons versus NCT01479465. Further, this was more pronounced in comparisons using the Gompertz extrapolation.

When applied in the economic model, cost-effectiveness outcomes were relatively similar due to the large beneficial impact of NIVO+IPI. Further, the impact of discounting minimises the longer-term benefits, decreasing the impact on the ICER. Hence, cost-effectiveness conclusions remain unchanged.

Table 2. MAIC output: Overall survival outcomes – exponential extrapolation

Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	107.55	4.68 (0.175)							
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	100.1	4.61 (0.431)	1.75 (0.434)	18.61	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	102.2	4.63 (0.189)	1.99 (0.194)	14.68	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	104.3	4.65 (0.187)	1.59 (0.220)	21.83	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	88.0	4.48 (0.200)	1.69 (0.211)	19.82	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	60.5	4.10 (0.243)	1.35 (0.248)	27.93	21. 92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	64.3	4.16 (0.292)	1.12 (0.335)	35.07	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	100.3	4.61 (0.239)	2.27 (0.254)	11.14	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	81.1	4.40 (0.363)	1.94 (0.430)	15.53	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	149.7	5.01 (0.204)	2.56 (0.214)	8.33	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	99.2	4.60 (0.240)	2.62 (0.312)	7.83	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	96.0	4.56 (0.335)	2.48 (0.588)	9.05	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	106.0	4.66 (0.209)	2.34 (0.246)	10.39	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	161.4	5.08 (0.196)	2.92 (0.209)	5.80	6.21

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Table 3. MAIC output: Overall survival outcomes - generalised gamma extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	158.91	5.07 (0.270)							
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	187.2	5.23 (0.557)	2.38 (0.559)	14.70	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	152.9	5.03 (0.285)	2.39 (0.288)	14.51	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	146.4	4.99 (0.276)	1.93 (0.299)	22.99	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	113.8	4.73 (0.365)	1.95 (0.371)	22.66	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	116.1	4.75 (0.333)	2.00 (0.336)	21.49	21. 92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	141.6	4.95 (0.534)	1.91 (0.559)	23.53	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	129.6	4.86 (0.470)	2.52 (0.478)	12.74	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	159.6	5.07 (0.475)	2.61 (0.529)	11.66	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	238.3	5.47 (0.363)	3.02 (0.369)	7.73	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	128.1	4.85 (0.471)	2.88 (0.511)	8.96	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	181.3	5.20 (0.490)	3.11 (0.688)	7.07	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	173.6	5.16 (0.237)	2.83 (0.269)	9.38	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	243.5	5.49 (0.388)	3.33 (0.395)	5.68	6.21

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Table 4. MAIC output: Overall survival outcomes – Gompertz extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	231.39	5.44 (0.246)							
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	246.4	5.51 (0.320)	2.66 (0.323)	16.26	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	231.0	5.44 (0.290)	2.81 (0.293)	13.98	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	212.5	5.36 (0.298)	2.31 (0.320)	23.06	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	198.9	5.29 (0.459)	2.51 (0.464)	18.87	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	198.6	5.29 (0.176)	2.54 (0.182)	18.29	21. 92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	185.7	5.22 (0.172)	2.18 (0.238)	26.13	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	106.0	4.66 (0.615)	2.32 (0.621)	22.67	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	227.3	5.43 (0.269)	2.97 (0.355)	11.92	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	260.8	5.56 (0.162)	3.11 (0.175)	10.29	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	105.4	4.66 (0.616)	2.68 (0.647)	15.85	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	241.5	5.49 (0.278)	3.40 (0.557)	7.73	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	234.3	5.46 (0.094)	3.13 (0.160)	10.12	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	262.6	5.57 (0.191)	3.41 (0.205)	7.67	6.21

Table 5. MAIC output: Overall survival outcomes – lognormal extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	189.25	5.24 (0.170)							
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	212.6	5.36 (0.366)	2.51 (0.369)	15.41	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	194.2	5.27 (0.179)	2.63 (0.183)	13.60	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	182.1	5.20 (0.181)	2.15 (0.215)	22.01	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	167.8	5.12 (0.230)	2.34 (0.239)	18.30	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	136.3	4.91 (0.271)	2.16 (0.275)	21.80	21. 92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	86.4	4.46 (0.311)	1.42 (0.352)	45.90	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	134.7	4.90 (0.303)	2.56 (0.315)	14.60	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	179.1	5.19 (0.266)	2.73 (0.352)	12.37	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	237.6	5.47 (0.114)	3.02 (0.132)	9.24	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	134.1	4.90 (0.304)	2.92 (0.363)	10.19	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	200.1	5.30 (0.226)	3.21 (0.533)	7.63	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	198.1	5.29 (0.170)	2.96 (0.214)	9.79	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	242.3	5.49 (0.115)	3.33 (0.136)	6.80	6.21

Table 6. MAIC output: Overall survival outcomes – log-logistic extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	Original
CheckMate 142	NIVO+IPI	119	168.13	5.12 (0.177)							
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	200.5	5.30 (0.200)	2.45 (0.205)	14.52	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	173.9	5.16 (0.193)	2.52 (0.198)	13.50	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	163.3	5.10 (0.211)	2.04 (0.241)	21.80	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	144.6	4.97 (0.210)	2.19 (0.220)	18.87	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	120.4	4.79 (0.178)	2.04 (0.184)	21. 92	21. 92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	85.2	4.44 (0.368)	1.40 (0.403)	41.40	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	113.4	4.73 (0.234)	2.39 (0.249)	15.41	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	163.4	5.10 (0.192)	2.64 (0.300)	12.05	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	229.9	5.44 (0.131)	2.99 (0.146)	8.48	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	112.8	4.73 (0.231)	2.75 (0.305)	10.77	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	185.6	5.22 (0.194)	3.14 (0.521)	7.31	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	181.8	5.20 (0.178)	2.88 (0.220)	9.47	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	235.5	5.46 (0.114)	3.30 (0.135)	6.21	6.21

Table 7. MAIC output: Overall survival outcomes – Weibull extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	151.99	5.02 (0.239)							
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	192.1	5.26 (0.431)	2.41 (0.433)	13.70	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	159.0	5.07 (0.271)	2.43 (0.274)	13.34	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	150.5	5.01 (0.266)	1.96 (0.290)	21.39	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	123.9	4.82 (0.315)	2.03 (0.322)	19.91	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	99.1	4.60 (0.334)	1.84 (0.337)	24.08	21. 92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	66.5	4.20 (0.321)	1.15 (0.360)	47.93	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	86.5	4.46 (0.350)	2.12 (0.360)	18.25	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	149.8	5.01 (0.347)	2.55 (0.417)	11.88	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	227.0	5.42 (0.172)	2.97 (0.184)	7.76	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	86.0	4.45 (0.352)	2.48 (0.404)	12.77	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	175.3	5.17 (0.304)	3.08 (0.571)	7.00	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	171.7	5.15 (0.244)	2.82 (0.276)	9.07	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	233.2	5.45 (0.173)	3.29 (0.187)	5.67	6.21

Table 8. MAIC output: Progression-free survival outcomes – exponential extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	69.8	4.25 (0.185)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	64.4	4.16 (0.226)	2.46 (0.229)	5.94	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	68.6	4.23 (0.220)	2.55 (0.224)	5.45	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	66.8	4.20 (0.217)	2.30 (0.246)	7.00	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	58.8	4.07 (0.189)	2.18 (0.194)	7.86	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	49.1	3.89 (0.202)	1.98 (0.207)	9.66	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	55.2	4.01 (0.512)	1.91 (0.526)	10.34	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	59.9	4.09 (0.189)	2.79 (0.220)	4.29	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	74.9	4.32 (0.189)	3.03 (0.270)	3.38	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	83.2	4.42 (0.187)	3.04 (0.739)	3.35	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	59.5	4.09 (0.190)	3.48 (0.193)	2.14	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	78.3	4.36 (0.189)	3.73 (0.211)	1.67	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	62.1	4.13 (0.241)	3.50 (0.330)	2.12	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	87.2	4.47 (0.222)	3.79 (0.225)	1.58	1.58

Table 9. MAIC output: Progression-free survival outcomes – generalised gamma extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	**Scenario**	**N**	**Mean survival outcomes**	**ln(mean) (se)**	**Adjustment set**	**ESS**	**Adjusted mean**	**Adjusted ln(mean) (se)**	**Δln(mean) (se)**	**Updated**	**A11**
CheckMate 142	NIVO+IPI	119	42.0	3.74 (0.468)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	127.3	4.85 (0.576)	3.15 (0.578)	1.81	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	39.2	3.67 (0.464)	1.99 (0.465)	5.74	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	36.6	3.60 (0.392)	1.70 (0.409)	7.68	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	33.1	3.50 (0.467)	1.61 (0.469)	8.42	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	62.3	4.13 (0.544)	2.22 (0.546)	4.58	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	24.3	3.19 (0.868)	1.09 (0.876)	14.16	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	80.8	4.39 (0.616)	3.09 (0.626)	1.91	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	101.3	4.62 (0.659)	3.33 (0.686)	1.51	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	40.6	3.70 (0.458)	2.32 (0.850)	4.13	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	78.1	4.36 (0.606)	3.75 (0.607)	0.98	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	92.1	4.52 (0.597)	3.89 (0.604)	0.86	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	30.5	3.42 (0.470)	2.78 (0.522)	2.60	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	37.8	3.63 (0.513)	2.95 (0.514)	2.19	1.58

Table 10. MAIC output: Progression-free survival outcomes – Gompertz extrapolation

	Study characteristics				Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)		ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	37.3	3.62 (0.525)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	85.2	4.44 (0.745)	2.74 (0.745)	2.40	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	36.5	3.60 (0.431)	1.92 (0.433)	5.48	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	33.9	3.52 (0.342)	1.62 (0.361)	7.36	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	32.4	3.48 (0.377)	1.59 (0.379)	7.62	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	37.0	3.61 (0.610)	1.70 (0.611)	6.84	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	23.6	3.16 (0.877)	1.06 (0.885)	12.93	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	33.8	3.52 (0.429)	2.22 (0.443)	4.05	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	156.3	5.05 (0.811)	3.76 (0.833)	0.87	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	35.3	3.56 (0.380)	2.18 (0.810)	4.22	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	33.6	3.51 (0.423)	2.91 (0.424)	2.03	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	68.5	4.23 (0.822)	3.60 (0.828)	1.02	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	29.8	3.40 (0.451)	2.76 (0.504)	2.35	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	34.7	3.55 (0.328)	2.87 (0.330)	2.13	1.58

Table 11. MAIC output: Progression-free survival outcomes – lognormal extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	107.5	4.68 (0.309)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	83.2	4.42 (0.521)	2.72 (0.522)	7.07	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	95.3	4.56 (0.306)	2.88 (0.308)	6.04	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	87.9	4.48 (0.341)	2.57 (0.360)	8.19	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	73.9	4.30 (0.298)	2.41 (0.301)	9.63	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	70.9	4.26 (0.332)	2.35 (0.336)	10.29	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	56.6	4.04 (0.632)	1.94 (0.644)	15.51	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	64.3	4.16 (0.277)	2.86 (0.299)	6.15	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	150.7	5.02 (0.518)	3.73 (0.552)	2.59	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	97.2	4.58 (0.365)	3.19 (0.803)	4.41	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	63.8	4.16 (0.279)	3.55 (0.281)	3.08	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	153.8	5.04 (0.583)	4.41 (0.590)	1.31	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	73.1	4.29 (0.368)	3.66 (0.431)	2.77	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	76.2	4.33 (0.393)	3.65 (0.394)	2.79	1.58

Table 12. MAIC output: Progression-free survival outcomes – log-logistic extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	84.3	4.43 (0.295)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	72.5	4.28 (0.519)	2.58 (0.520)	6.36	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	75.8	4.33 (0.274)	2.65 (0.277)	5.95	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	69.4	4.24 (0.289)	2.34 (0.311)	8.14	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	62.5	4.14 (0.252)	2.25 (0.257)	8.92	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	61.6	4.12 (0.294)	2.21 (0.298)	9.29	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	46.0	3.83 (0.613)	1.73 (0.624)	14.96	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	58.8	4.07 (0.248)	2.77 (0.272)	5.27	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	137.9	4.93 (0.540)	3.64 (0.574)	2.22	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	76.9	4.34 (0.336)	2.96 (0.790)	4.37	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	58.2	4.06 (0.249)	3.46 (0.251)	2.65	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	137.0	4.92 (0.593)	4.29 (0.601)	1.15	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	60.9	4.11 (0.331)	3.48 (0.400)	2.60	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	65.9	4.19 (0.351)	3.51 (0.353)	2.53	1.58

Table 13. MAIC output: Progression-free survival outcomes – generalised gamma extrapolation

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	58.9	4.08 (0.330)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	53.8	3.98 (0.576)	2.29 (0.577)	6.00	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	52.6	3.96 (0.288)	2.29 (0.291)	5.99	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	48.5	3.88 (0.284)	1.98 (0.306)	8.14	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	43.1	3.76 (0.244)	1.87 (0.248)	9.05	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	42.9	3.76 (0.307)	1.84 (0.311)	9.32	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	31.5	3.45 (0.653)	1.35 (0.664)	15.28	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	41.4	3.72 (0.234)	2.42 (0.259)	5.23	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	125.4	4.83 (0.586)	3.54 (0.617)	1.70	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	53.7	3.98 (0.341)	2.60 (0.792)	4.38	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	41.0	3.71 (0.235)	3.11 (0.237)	2.63	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	121.5	4.80 (0.635)	4.17 (0.642)	0.91	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	40.6	3.70 (0.309)	3.07 (0.383)	2.73	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	47.3	3.86 (0.320)	3.18 (0.322)	2.46	1.58

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

Addendum to clarification questions

December 2020

1. **Please clarify if the revised company base case includes the revisions to the matching-adjusted indirect comparison (MAIC) given in response to clarification question A11 (changing comparator studies and adjusting for additional covariates). For example, is the company's base case ICER for nivolumab plus ipilimumab (NIVO+IPI) vs trifluridine-tipiracil (Tri/Tip) £13,783 or £13,367? The ERG is unclear why the results in "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking Base Case" and "Copy of Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking CQ A11" do not match. If the company base case has been revised, please also provide revised scenario analyses (scenarios outlined in Section B.3.8.3 of Document B).**

The company base case analysis has not been revised in response to clarification question A11. The base case analysis remains as detailed in the company submission. It is acknowledged that there are alternative methodologies to undertake the analysis. However, for the reasons outlined in the clarifications response, BMS believe that the base case analysis provided in the company submission uses the most informative form of the MAIC. In particular, use of KRAS/BRAF status as a covariate, as requested by the ERG, has limited value.

Hence, the economic model labelled "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking Base Case" provides results for the company base case, including the functionality requested in the ERG clarifications. The economic model labelled "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking CQ A11" provides results for the response to ERG clarification question A11. This is summarised in Table 1.

Table 1. Sources of ICER versus trifluridine-tipiracil

Source	ICER	Economic model
Company submission base case analysis	£13,367	Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking Base Case
ERG clarification questions A11 response	£13,783	Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking CQ A11

2. **In response to clarification questions B3 and B9, the ERG is referred to the model "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking". One of the models provided to the ERG has a similar title, "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking Base Case". In this model, the ERG cannot find the progression-free survival (PFS), overall survival (OS) or time on treatment (ToT) profiles requested in clarification questions B3 and B9. Additionally, the ERG cannot run**

any scenarios outlined in Section B.3.8.3 of Document B in this model. Survival profiles only include:

- **Base Case: Tri/Tip PFS**
- **Base Case: Tri/Tip OS**
- **Base Case: Tri/Tip ToT**
- **Base Case: BSC PFS**
- **Base Case: BSC OS**
- **Base Case: folinic acid, fluorouracil and oxaliplatin (FOLFOX) PFS**
- **Base Case: FOLFOX OS**
- **Base Case: FOLFOX ToT**
- **Base Case: folinic acid, fluorouracil and irinotecan (FOLFIRI) PFS**
- **Base Case: FOLFIRI OS**
- **Base Case: FOLFIRI ToT**
- **Base Case: irinotecan (Iri) PFS**
- **Base Case: Iri OS**
- **Base Case: Iri ToT**
- **Base Case: raltitrexed (Ralt) PFS**
- **Base Case: Ralt OS**
- **Base Case: Ralt ToT**

Please provide a model with the profiles requested in clarification questions B3 and B9 and all other scenarios outlined in Section B.3.8.3 of Document B, in addition to the revised assumptions mentioned in clarification question A11.

The economic model "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking" was submitted with the original company submission. In order to provide all scenarios required by the ERG as part of the clarification questions, scenario analyses were removed from the economic models provided in response, which is why newly submitted models do not include scenario analyses.

A detailed explanation for selecting these model settings is provided below. Please note that this analysis is provided in the economic model "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking" (i.e., the economic model submitted with the original submission).

ERG clarification question B3: Selection of fully parametric models for NIVO+IPI

This example explains how to select an alternative extrapolation study for the NIVO+IPI PFS. A similar approach is required to select PFS, OS and ToT. A screenshot is provided below for ease of reference.

On the model control sheet, under Treatment Arm, select the PFS profile dropdown box and scroll up to "Section B.3.8.3.2: NIVO+IPI FP PFS Gen Gamma" profile, which is the first of the fully parametric fits. Within the dropdown box, fully parametric fits are denoted by the abbreviation "FP" and semi-parametric fits are denoted by the abbreviation "SP".

Fully parametric models have not been provided where there is evidence of a poor fit to the underlying Kaplan-Meier data, as outlined in Document B, Section B.3.3.2.

Please note that this analysis is provided in the economic model "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking" (i.e., the economic model submitted with the original submission).

ERG clarification question B9: Selection of alternative indirect evidence sources

This example explains how to select an alternative study for the trifluridine-tipiracil PFS. A similar approach is required to select PFS, OS and ToT for all comparators and all evidence sources. A screenshot is provided below for ease of reference and input profile labels applied in the economic model are detailed in Table 2.

On the model control sheet, under Control Arm, select the PFS profile dropdown box and scroll down to "Section B.3.8.3.4: Alt studies – Tri/Tip PFS" profile, which is the first of the alternative comparator evidence sources. All inputs required for running the scenarios in Section B.3.8.3.4 of the company submission are labelled as such.

Please note that this analysis is provided in the economic model "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking" (i.e., the economic model submitted with the original submission).

Table 2. Alternative measures of comparator efficacy

Scenario	Efficacy input vs model output	Outcome	Trifluridine-tipiracil	BSC	FOLFOX	FOLFIRI	Irinotecan	Raltitrexed
Base case	Source: MAIC base case analysis		RECOURSE EU population	RECOURSE EU population	CONFIRM2	VELOUR	PICCOLO	Ugidos
	Efficacy input	PFS input profile label	Base Case: Tri/Tip PFS	Base Case: BSC PFS	Base Case: FOLFOX PFS	Base Case: FOLFIRI PFS	Base Case: Iri PFS	Base Case: Ralt PFS
		OS input profile label	Base Case: Tri/Tip OS	Base Case: BSC OS	Base Case: FOLFOX OS	Base Case: FOLFIRI OS	Base Case: Iri OS	Base Case: Ralt OS
	Model output	Inc QALYs	■	■	■	■	■	■
		Inc Costs	■	■	■	■	■	■
		ICER	£13,366	£14,211	£14,839	£14,930	£15,022	£15,346
Alternative sources of comparator data	Source: MAIC scenario analysis		RECOURSE US population	RECOURSE US population	NA	RAISE	EPIC	NA
	Efficacy input	PFS input profile label	Section B.3.8.3.4: Alt Studies - Tri/Tip PFS	Section B.3.8.3.4: Alt Studies - BSC PFS	Not applicable	Section B.3.8.3.4: Alt Studies - FOLFIRI PFS	Not provided	Not applicable
		OS input profile label	Section B.3.8.3.4: Alt Studies - Tri/Tip OS	Section B.3.8.3.4: Alt Studies - BSC OS	Not applicable	Section B.3.8.3.4: Alt Studies - FOLFIRI OS	Not provided	Not applicable
	Model output	Inc QALYs	■	■	NA	■	■	NA
		Inc Costs	■	■	NA	■	■	NA
		ICER	£13,418	£14,240	NA	£15,183	£14,673	NA
Unadjusted survival outcomes	Source: unadjusted comparison versus single studies		RECOURSE EU population	RECOURSE EU population	CONFIRM2	VELOUR	PICCOLO	Ugidos
	Efficacy input	PFS input profile label	Section B.3.8.3.4: Unadjusted - Tri/Tip PFS	Section B.3.8.3.4: Unadjusted - BSC PFS	Section B.3.8.3.4: Unadjusted - FOLFOX PFS	Section B.3.8.3.4: Unadjusted - FOLFIRI PFS	Not provided	Not provided
		OS input profile label	Section B.3.8.3.4: Unadjusted - Tri/Tip OS	Section B.3.8.3.4: Unadjusted - BSC OS	Section B.3.8.3.4: Unadjusted - FOLFOX OS	Section B.3.8.3.4: Unadjusted - FOLFIRI OS	Not provided	Not provided
	Model output	Inc QALYs	■	■	■	■	■	■
		Inc Costs	■	■	■	■	■	■
		ICER	£13,304	£14,177	£15,056	£14,993	£14,882	£13,937
Pooled survival outcomes (medians)	Source: Pooled median SLR outcomes (Table 14 of company submission) – Not provided in economic model							
	Efficacy input	PFS rate	0.2656	0.4053	0.1423	0.1513	0.2003	0.2900
		OS rate	0.0879	0.1146	0.0581	0.0544	0.0664	0.1097
	Model output	Inc QALYs	■	■	■	■	■	■
		Inc Costs	■	■	■	■	■	■
		ICER	£13,393	£14,305	£15,117	£15,265	£14,906	£13,964

BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; IPI: ipilimumab; NR: not reported; OS: overall survival; PFS: progression-free survival

3. **The hazard profiles for PFS and ToT are similar. Therefore, the ERG is surprised that this consistency is not followed through into the spline-based models (Figures 38 and 39 of clarification question B4). Please either explain why there are no visible knots for ToT, or re-evaluate the number or location of the knots for ToT to better reflect the Kaplan–Meier (KM) data. Please also provide the Akaike information criterion (AIC) and Bayesian information criterion (BIC) fit statistics for these models.**

As noted in the clarification response, the spline models were optimised using a two-step process. For each model with internal knots, the location and value of these knots was optimised by a 2-step optimisation procedure. The location of the knots was free to vary within the limits of time domain of the observed event data for the optimal placement to be achieved. Within each optimisation step, the location of the knots was varied and the knot values fitted by maximum likelihood, attempting to find the global maximum likelihood set of knot location and values. The models produced were examined for physical plausibility (e.g., hazards positive at all times) and of the plausible models (in line with TSD 14 guidance in fit), the best fitting was selected, considerate of overfitting by Akaike Information Criterion (AIC). In both cases, these models had 2 internal knots.

The AIC and knot placement for PFS and time on treatment are detailed in Table 3. As detailed in the response to clarification question B4, both models are two knot splines. Further, both use a similar scheduling for the first knot in the data. However, AIC is not improved by increasing knots for time on treatment curves, whereas this is the case for PFS. Additionally, there are significant differences in placement of the second knot. Where the PFS curve applied a knot in the latter period of the data, reflecting a change in the hazard profile later in the data. By contrast, the time on treatment curve applies two early knots, reflecting a more rapid change in hazard earlier in the data.

Differences between PFS and time on treatment can be expected given the underlying biological mechanisms. In contrast with PFS, patients may discontinue NIVO+IPI due to lack of clinical benefit or due to adverse events. Hence, although the hazard profiles for PFS and time on treatment are similar, there are underlying differences that should also be reflected when modelling the data.

Table 3. Comparison of spline models for PFS and time on treatment

Number of knots	Log-likelihood	AIC	Knot locations			
			1	2	3	4
Investigator-assessed PFS						
0	-229.14	462.29	-2.029	3.728	NA	NA
1	-224.65	455.31	-2.029	0.446	3.728	NA
2	-219.64	447.28	-2.029	1.019	3.039	3.728
Time on treatment						
0	-292.82	589.63	-3.416	3.473	NA	NA
1	-292.75	591.50	-3.416	-0.394	3.473	NA
2	-292.00	591.99	-3.416	0.740	0.748	3.473

4. Please clarify which parametric survival distributions have been used to inform the adjusted Checkmate 142 data in response to clarification question B12.

The extrapolations for NIVO+IPI matched that for the comparator in each of the scenarios, replicated below.

Table 4. Scenario analysis: comparator parametric distributions

Comparator	Study	OS		PFS	
		Extrapolation	Mean outcome	Extrapolation	Mean outcome
Trifluridine-tipiracil	RECOURSE EUR	Lognormal	10.4	Generalised gamma	3.7
	RESCOURSE USA	Lognormal	11.7	Generalised gamma	3.6
	TERRA	Log-logistic	11.6	Generalised gamma	4.0
BSC	RECOURSE EUR	Generalised gamma	7.2	Log-logistic	1.8
	RECOURSE USA	Generalised gamma	8.1	Log-logistic	1.9
	LUNECOLON 1	Generalised gamma	10.2	Generalised gamma	1.9
	TERRA	Lognormal	8.7	Log-logistic	2.0
FOLFOX	CONFIRM2	Lognormal	17.3	Lognormal	5.5
	NO16967	Generalised gamma	14.0	Weibull	5.4
	CAPRIGOIM	Log-logistic	21.2	Log-logistic	6.7
FOLFIRI	VELOUR	Generalised gamma	15.7	Lognormal	6.8
	RAISE	Generalised gamma	16.2	Lognormal	6.6
	NCT01479465	Lognormal	21.0	Lognormal	8.2
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; IPI: ipilimumab; NR: not reported; OS: overall survival; PFS: progression-free survival					

5. In response to clarification question B5 for ToT, please provide an executable option in the economic model for a piecewise model using 2.99 months of KM data followed by an exponential extrapolation.

Given the current timelines, the suggested extrapolation (semi-parametric model with Kaplan-Meier to 2.99 months followed by exponential fit) has not been provided for the following reasons:

- This extrapolation does not provide a good fit to the observed hazard profile, which strongly indicate decreasing hazard over time.
- It is more conservative compared with the applied log-logistic fit, so would have limited impact on cost-effectiveness conclusions.
- All extrapolations applying Kaplan-Meier to 2.99 months provide a poor fit to the observed data, particularly when compared with the 6.44-month semi-parametric extrapolations (Figure 1 and Figure 2, respectively).

Figure 1. Time on treatment extrapolation using data cut at 2.99 months

Figure 2. Time on treatment: CheckMate 142 NIVO+IPI – parametric extrapolations

6. Given that no details were provided around the composition of subsequent therapy in TA405, the composition of subsequent therapy in TA405 may be outdated. The ERG does not consider inflating the cost to a 2018/19 cost year addresses this potential issue. Please provide a scenario using a composition which is reflective of NHS practice today, ensuring subsequent treatment costs reflect the time in the progressed disease (PD) health state (as noted in clarification question B26). Please also discuss the differences between subsequent treatments received in Checkmate 142 and subsequent treatments available to patients in the NHS.

There is an absence of evidence to inform subsequent treatment in previously treated CRC, and even less evidence in previously treated MSI-H/dMMR mCRC. In the absence of this evidence, published sources have been searched for plausible assumptions.

Trifluridine-tipiracil was appraised by NICE in 2016, during TA405.[1] Since that time no new CRC therapies have been appraised by NICE and there has been no major practise-changing research published. This is confirmed by NG151,[2] published in January 2020, which states: "Guidance on systemic anti-cancer therapy for people with metastatic colorectal cancer is covered by NICE technology appraisals, which were not updated by this guideline. The committee did not review the technology appraisals. The technology appraisals should be used when appropriate to guide the choice of systemic anti-cancer therapy." Further, NG151 suggests that the NICE pathway on colorectal cancer should be consulted for advice on systemic anti-cancer therapy for CRC.

Based on this evidence, TA405 is the best available evidence to inform subsequent treatment. This assumption has been assessed through scenario analysis (Section B.3.8.3.3 of the company submission) and deterministic sensitivity analysis (Section B.3.8.2 of the company submission) in order to assess the impact of this assumption.

Subsequent treatments in CheckMate 142 are discussed in Section B.3.5.1.4 of the company submission, with Table 42 reproduced below as Table 5. As discussed in the company submission, only 17 patients (14.3%) received a subsequent systemic therapy. Of those patients, the most common therapies received were relevant to UK clinical practice, including irinotecan, oxaliplatin, fluoropyrimidine and trifluridine-tipiracil. However, some patients received VEGF inhibitors (two patients), regorafenib (four patients), investigational agents (four patients), lapatinib (one patient), trametinib (one patient) and trastuzumab (one patient). Additionally, two patients received EGFR inhibitors, which are not recommended in the UK in the second-line setting. Despite this, the trial can be considered relevant to the UK patient population, as only a small proportion of the CheckMate142 population received subsequent therapy.

Because of these limitations, CheckMate 142 may not be useful to inform subsequent therapy in the economic model. Hence, use of TA405 may be considered conservative in the NIVO+IPI arm.

Table 5. CheckMate 142: subsequent cancer therapy (February 2019 database lock)[3]

	Overall population (n = 119) n (%)
Systemic therapy	██████
Oxaliplatin	███
Irinotecan	███
5-FU (fluorouracil, capecitabine)	███
VEGF inhibitors	███
EGFR inhibitors	███
Regorafenib	███
Trifluridine-tipiracil	███
Investigational anti-cancer therapies	███
Nivolumab	███
FLUR/LEUCO/OXAL	███
Lapatinib	███
Trametinib	███
Trastuzumab	███
Calcium levofolinate	███
Folinic acid	███
Leucovorin	███
Patients may receive more than one therapy	

7. **According to NICE DSU Technical Support Document (TSD) 18, all possible characteristics should be adjusted for in an unanchored comparison. As such, please reconsider the decision not to provide cost-effectiveness results based on all covariates (clarification questions A12 and B1). The ERG appreciates that these results will be highly uncertain as they will be based on a low effective study size.**

   a. **As a minimum, please provide these analyses for the following:**
      i. **FOLFOX - CONFIRM**
      ii. **FOLFIRI - RAISE and VELOUR**
      iii. **Trifluridine/tipiracil - RECOURSE**
      iv. **Best supportive care (BSC) - RECOURSE**
   b. **Please provide data adjusting for all covariates for RECOURSE, and provide an explanation for why the adjusted data were not presented for RECOURSE in the clarification response Table 40 and 41.**

The analysis using the full set of variates cannot be considered informative and produce results that are notably spurious, lacking face validity or clinical plausibility.

Table 6 and Table 7 summarise outcomes from the MAIC analyses. As can be seen, outcomes when applying all covariates lack face validity, due to the low effective sample size, denoted by red values. Mean OS for trifluridine-tipiracil is estimated to be 32.2 months, which is clinically implausible and is not aligned to clinical opinion. Similarly, mean OS for

FOLFIRI using all clinical covariates ranged from 22.7 months to 38.9 months. Clinical experts consider life expectancy in this population to be considerably shorter than 24 months, so that these outcomes cannot be considered to have face validity.

In the clarification questions, the ERG quotes the NICE DSU TSD 18, which recommends that "For an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables." On this basis, the ERG affirm that analyses should adjust for all effect modifiers and prognostic variables, as this will provide "the most accurate (although less precise) estimate for each of the comparisons." However, unanchored MAICs have to make trade-offs between effective sample size and the number of adjustment variables, and the decision for how many variables to include in the analysis is a key challenge[4]; to overcome this challenge, the company adopted a data-driven approach to maximising the bias reduction whilst minimising adjustment to "noise" terms. In this context, "noise" terms are those which, whilst supposed as potentially outcomes modifying, have weak conditional correlation with outcomes within the index trial data, and so in practice their effect is minimal for bias reduction, and may even be contrary to their true outcome modification direction as there was an insufficient random sample to determine the true effect. To avoid this, forward-selection of variables able to improve the predictive accuracy of semi-parametric models formed within the trial data was undertaken

Outputs for the RECOURSE analysis are not provided because the effective study size reduced to zero during the analysis. As such, it was not feasible to provide outcomes.

Table 6. Summary of comparator overall survival outcomes from MAIC analyses

Comparator	Study	Unadjusted study		Company submission MAIC		A11 MAIC analysis (limited covariates)		A12 MAIC analysis (all covariates)	
		Study size	Mean survival outcomes (months)	ESS	Mean survival outcomes (months)	ESS	Mean survival outcomes (months)	ESS	Mean survival outcomes (months)
FOLFOX	CONFIRM2	429	17.3	75.9	15.65	21.4	14.5	18.6	16.8
	NO16967	314	14.0	NA	NA	108.2	13.5	12.8	14.4
	CAPRI-GOIM	79	21.2	NA	NA	98.6	21.8	*6.4*	*36.6*
FOLFIRI	RAISE	536	16.2	98.4	17.19	91.1	18.9	*8.8*	*22.7*
	VELOUR	614	15.7	96.8	15.3	57.4	21.9	*17.5*	*31.8*
	NCT01479465	80	21.0	NA	NA	*19.7*	*41.4*	*18.2*	*38.9*
Trifluridine/ tipiracil	RECOURSE/EUR	271	10.4	96.5	10.86	63.2	15.4	NA	NA
	RECOURSE/USA	64	11.7	106	11.7	33.5	12.1	NA	NA
	TERRA	271	11.6	NA	NA	92.5	8.5	*5.7*	*32.2*
Best supportive care	RECOURSE/EUR	132	7.2	97.5	7.55	64.2	10.8	NA	NA
	RECOURSE/USA	35	8.1	106.4	8.13	36.1	7.3	NA	NA
	LUMECOLON1	382	10.2	NA	NA	79.5	9.5	*4.4*	*12.2*
	TERRA	135	8.7	NA	NA	85.1	6.2	*13.0*	*9.9*

Table 7. Summary of comparator progression-free survival outcomes from MAIC analyses

Comparator	Study	Unadjusted study		Company submission MAIC		A11 MAIC analysis (limited covariates)		A12 MAIC analysis (all covariates)	
		Study size	Mean survival outcomes (months)	ESS	Mean survival outcomes (months)	ESS	Mean survival outcomes (months)	ESS	Mean survival outcomes (months)
FOLFOX	CONFIRM2	429	5.47	75.9	4.49	21.4	5.94	18.6	5.02
	NO16967	314	5.36	NA	NA	108.2	5.45	*12.8*	*11.68*
	CAPRI-GOIM	79	6.7	NA	NA	98.6	7	*6.4*	*18.7*
FOLFIRI	RAISE	536	6.62	98.4	7.54	91.1	7.86	*8.8*	*12.42*
	VELOUR	614	6.79	96.8	6.33	57.4	9.66	*17.5*	*11.56*
	NCT01479465	80	8.17	NA	NA	*19.7*	*10.34*	*18.2*	*10.85*
Trifluridine/ tipiracil	RECOURSE/EUR	271	3.68	96.5	4.19	63.2	4.29	NA	NA
	RECOURSE/USA	64	3.63	106	3.7	33.5	3.38	NA	NA
	TERRA	271	3.99	NA	NA	92.5	3.35	*5.7*	*6.81*
Best supportive care	RECOURSE/EUR	132	1.83	97.5	2.1	64.2	2.14	NA	NA
	RECOURSE/USA	35	1.87	106.4	1.9	36.1	1.67	NA	NA
	LUMECOLON1	382	1.88	NA	NA	79.5	2.12	*4.4*	*1.76*
	TERRA	135	1.97	NA	NA	85.1	1.58	*13*	*2.11*

Table 8. MAIC output: Overall survival outcomes applying all covariates

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)		ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	168.13	5.12 (0.177)							
FOLFOX											
CONFIRM-2	Base case	429	17.32	2.85 (0.048)	All	18.6	173.7	5.16 (0.319)	2.31 (0.322)	16.76	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	All	12.8	162.9	5.09 (0.431)	2.46 (0.433)	14.41	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	All	6.4	97.2	4.58 (0.693)	1.52 (0.703)	36.64	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	All	8.8	120.4	4.79 (NA)	2.00 (NA)	22.66	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	All	17.5	82.9	4.42 (0.279)	1.66 (0.282)	31.82	21.92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	All	18.2	90.6	4.51 (0.378)	1.46 (0.412)	38.91	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	All	NA	NA	NA	NA	NA	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	All	NA	NA	NA	NA	NA	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	All	5.7	60.5	4.10 (0.805)	1.65 (0.808)	32.22	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	All	NA	NA	NA	NA	NA	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	All	NA	NA	NA	NA	NA	7.31
LUME-Colon 1	Scenario	382	10.24	2.33 (0.129)	All	4.4	141.4	4.95 (0.679)	2.63 (0.691)	12.18	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	All	13.0	147.8	5.00 (0.537)	2.83 (0.542)	9.90	6.21

Table 9. MAIC output: Progression-free survival outcomes applying all covariates

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (se)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (se)	Δln(mean) (se)	Updated	A11
CheckMate 142	NIVO+IPI	119	69.8	4.25 (0.185)							
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	All	18.6	76.1	4.33 (0.392)	2.63 (0.394)	5.02	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	All	12.8	32.0	3.47 (0.540)	1.79 (0.542)	11.68	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	All	6.4	25.0	3.22 (0.673)	1.32 (0.683)	18.70	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	All	8.8	37.2	3.62 (NA)	1.73 (NA)	12.42	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	All	17.5	41.0	3.71 (0.289)	1.80 (0.293)	11.56	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	All	18.2	52.6	3.96 (0.434)	1.86 (0.450)	10.85	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	All	NA	NA	NA	NA	NA	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	All	NA	NA	NA	NA	NA	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	All	5.7	40.9	3.71 (1.133)	2.33 (1.340)	6.81	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	All	NA	NA	NA	NA	NA	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	All	NA	NA	NA	NA	NA	1.67
LUME-Colon 1	Scenario	382	1.88	0.63 (0.226)	All	4.4	74.6	4.31 (1.013)	3.68 (1.038)	1.76	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	All	13.0	65.2	4.18 (0.735)	3.50 (0.736)	2.11	1.58

However, the economic models provided to the ERG have the functionality to run the analysis if required. This can be undertaken in any model as required; an example is provided using "Nivo+Ipi MSI-H mCRC _NICE STA CEM CiC-AiC Marking Base Case".

On the model control tab, under Treatment Input, click the button marked "Edit Survival Curves".

On the survival tab, scroll down to the required profile; for this example, the trifluridine-tipiracil output has been updated to reflect the PFS MAIC output using the TERRA study. Under "Δ Ln(Mean)" (Column E), update using the value in the Δ Ln(Mean) column of Table 8 and Table 9. For "SE" (Column G), use the SE value in the above tables. For "Reference" (Column H), update using the NIVO+IPI value for Ln(Mean). The used value is derived using these inputs. An example is in the below screenshot.
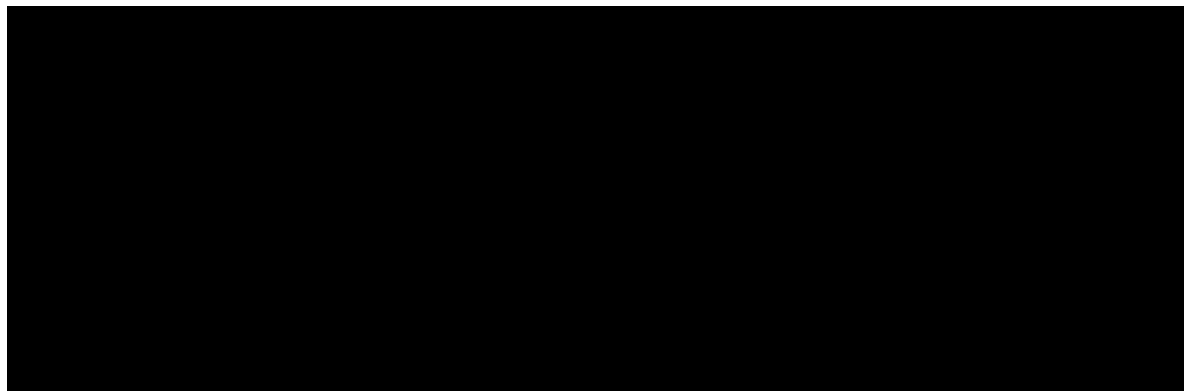
8. **The ERG would like to thank the company for their additional clarification response which makes the extrapolation for NIVO+IPI in the economic model consistent with the extrapolation method in the MAIC. In addition to the 6.44-month semi-parametric fits, can the MAIC analyses and cost-effectiveness results also be provided using the NIVO+IPI extrapolations listed below:**

   a. **Scenario 1:**
      i. **PFS: piecewise model, KM to 2.99 months followed by an exponential distribution (clarification question B5)**
      ii. **OS: piecewise model, KM to 2.99 months followed by a log logistic distribution (clarification question B5)**
   b. **Scenario 2:**

  i. **PFS: spline-based model (clarification question B4)**
  ii. **OS: piecewise model, KM to 2.99 months followed by a log logistic distribution (clarification question B5)**
 c. **Scenario 3:**
  i. **PFS: piecewise model, KM to 2.99 months followed by an exponential distribution (clarification question B5)**
  ii. **OS: fully parametric model, log logistic distribution**
 d. **Scenario 4:**
  i. **PFS: spline-based model (clarification question B4)**
  ii. **OS: fully parametric model, log logistic distribution**

For each scenario can the company:

- **Use their preferred trial for each comparator, plus RAISE for FOLFIRI, and their preferred set of covariates (clarification question A11)**
- **Use the trials outlined in question 7 above and adjust for all covariates**
- **Provide MAIC results in a similar format to Tables 22 and 23 of the clarification responses**
- **Extrapolate ToT based on a piecewise model using 2.99 months of KM data followed by a log logistic extrapolation (clarification question B5)**
- **Include an option in the same model to extrapolate time-to-treatment discontinuation (TTD) using a spline-based model (including any revisions to that given in response to CQ B4) and a piecewise model using 2.99 months of KM data followed by an exponential extrapolation**

Please also include the aforementioned extrapolations as executable options in the model for the naive comparisons.

As outlined in the company submission, the clarification response and the subsequent clarification response, a semi-parametric approach using extrapolation from 6.44 months was considered the most appropriate approach to long-term extrapolation of outcomes. As such, the outcomes from this analysis can be considered exploratory and are provided to allow exploration of the uncertainty in the analysis.

In particular, the OS hazard functions demonstrated in Appendix M Figure 15 cannot be adequately described by a standard parametric model. Of the fully parametric models, the best fit is provided by the Gompertz survival function, rather than the log-logistic functions. Given the poor fit to the data, it is unclear why the ERG has requested the log-logistic function in its analysis. However, this is provided to assess the impact of using a highly conservative outcome that cannot be considered plausible, particularly in the context of the updated database lock.

Results from the requested MAICs are provided in Table 10 to Table 17. The outcomes using all covariates are also provided but are not implemented in the economic model due to the implausible outcomes predicted by the analysis.

Time on treatment has been used in the company submission (defined as time from treatment initiation to last dose for patients who have discontinued treatment). This is more appropriate than time to discontinuation (defined as time from treatment initiation to date of

discontinuation) because date of discontinuation may overestimate time on treatment and will not reflect the patient experience of actual doses of therapy received. Hence, this analysis has not been undertaken.

Table 10. MAIC output: Overall survival outcomes – KM to 2.99 months then log-logistic (scenario 1 and 2)

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (SE)		ESS	Adjusted mean	Adjusted ln(mean) (SE)	Δln(mean) (SE)	Updated	A11
NIVO+IPI											
CheckMate 142	NIVO+IPI	119									
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	159.1	5.07 (0.395)	2.22 (0.398)	18.13	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	160.8	5.08 (0.166)	2.44 (0.171)	14.47	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	151.0	5.02 (0.160)	1.96 (0.198)	23.37	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	137.0	4.92 (0.188)	2.13 (0.199)	19.74	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	94.2	4.55 (0.259)	1.79 (0.263)	27.77	21.92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	82.0	4.41 (0.301)	1.36 (0.343)	42.60	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	145.2	4.98 (0.309)	2.64 (0.321)	11.92	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	128.6	4.86 (0.301)	2.40 (0.380)	15.17	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	216.2	5.38 (0.118)	2.93 (0.135)	8.94	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	147.2	4.99 (0.301)	3.01 (0.361)	8.17	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	147.4	4.99 (0.263)	2.90 (0.550)	9.12	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	172.9	5.15 (0.151)	2.83 (0.198)	9.87	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	223.2	5.41 (0.114)	3.24 (0.135)	6.50	6.21

Table 11. MAIC output: Progression-free survival outcomes – KM to 2.99 months followed by exponential (Scenario 1 and 3)

Study	Scenario	N	Mean survival outcomes	ln(mean) (SE)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (SE)	Δln(mean) (SE)	Updated	A11
NIVO+IPI											
CheckMate 142	NIVO+IPI	119									
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	49.3	3.90 (0.468)	2.20 (0.469)	7.08	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	63.2	4.15 (0.181)	2.47 (0.185)	5.40	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	64.4	4.17 (0.179)	2.26 (0.213)	6.63	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	57.3	4.05 (0.189)	2.16 (0.194)	7.36	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	44.8	3.80 (0.254)	1.89 (0.259)	9.65	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	43.9	3.78 (0.481)	1.68 (0.496)	11.86	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	61.1	4.11 (0.217)	2.81 (0.244)	3.83	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	60.3	4.10 (0.400)	2.81 (0.444)	3.84	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	74.1	4.31 (0.207)	2.92 (0.745)	3.43	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	60.6	4.10 (0.218)	3.50 (0.220)	1.92	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	63.8	4.16 (0.368)	3.53 (0.379)	1.87	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	57.4	4.05 (0.185)	3.42 (0.292)	2.09	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	75.1	4.32 (0.219)	3.64 (0.222)	1.68	1.58

Table 12. MAIC output: Progression-free survival outcomes – spline model (Scenario 2 and 4)

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (SE)		ESS	Adjusted mean	Adjusted ln(mean) (SE)	Δln(mean) (SE)	Updated	A11
NIVO+IPI											
CheckMate 142	NIVO+IPI	119									
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	Primary	21.4	60.8	4.11 (0.602)	2.41 (0.603)	4.83	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	Secondary	108.2	49.2	3.90 (0.290)	2.22 (0.293)	5.85	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	Secondary	98.6	44.3	3.79 (0.256)	1.89 (0.281)	8.12	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	Secondary	91.1	38.8	3.66 (0.240)	1.77 (0.244)	9.18	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	Secondary	57.4	40.4	3.70 (0.370)	1.78 (0.373)	9.03	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	Primary	19.7	35.2	3.56 (0.658)	1.46 (0.669)	12.46	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	Secondary	63.2	35.1	3.56 (0.225)	2.26 (0.251)	5.63	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	Secondary	33.5	111.9	4.72 (0.522)	3.43 (0.557)	1.74	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	Secondary	92.5	60.1	4.10 (0.328)	2.71 (0.787)	3.57	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	Secondary	64.2	34.7	3.55 (0.221)	2.94 (0.223)	2.83	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	Secondary	36.1	104.3	4.65 (0.513)	4.02 (0.521)	0.97	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	Secondary	79.5	40.0	3.69 (0.282)	3.06 (0.361)	2.53	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	Secondary	85.1	60.0	4.09 (0.330)	3.41 (0.332)	1.77	1.58

Table 13. MAIC output: Overall survival outcomes – fully parametric log-logistic (scenario 3 and 4)

Study	Scenario	N	Mean survival outcomes	ln(mean) (SE)	Adjustment set	ESS	Adjusted mean	Adjusted ln(mean) (SE)	Δln(mean) (SE)	Updated	A11
	Study characteristics				Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
NIVO+IPI											
CheckMate 142	NIVO+IPI	119									
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	Primary	21.4	128.1	4.85 (0.390)	2.00 (0.393)	19.10	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	Secondary	108.2	134.5	4.90 (0.161)	2.27 (0.166)	14.66	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	Secondary	98.6	132.5	4.89 (0.157)	1.83 (0.195)	22.60	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	Secondary	91.1	113.6	4.73 (0.181)	1.95 (0.192)	20.19	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	Secondary	57.4	86.1	4.46 (0.253)	1.70 (0.257)	25.78	21.92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	Primary	19.7	88.0	4.48 (0.298)	1.43 (0.340)	33.67	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	Secondary	63.2	122.8	4.81 (0.212)	2.47 (0.229)	11.96	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	Secondary	33.5	113.6	4.73 (0.318)	2.27 (0.393)	14.56	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	Secondary	92.5	177.5	5.18 (0.139)	2.73 (0.154)	9.23	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	Secondary	64.2	121.2	4.80 (0.211)	2.82 (0.290)	8.42	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	Secondary	36.1	138.8	4.93 (0.271)	2.84 (0.554)	8.22	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	Secondary	79.5	137.2	4.92 (0.161)	2.59 (0.206)	10.55	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	Secondary	85.1	185.2	5.22 (0.136)	3.06 (0.154)	6.64	6.21

Table 14. MAIC output: Overall survival outcomes – KM to 2.99 months then log-logistic (all covariates)

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (SE)		ESS	Adjusted mean	Adjusted ln(mean) (SE)	Δln(mean) (SE)	Updated	A11
NIVO+IPI											
CheckMate 142	NIVO+IPI	119									
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	All	18.6	157.7	5.06 (0.452)	2.21 (0.454)	18.29	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	All	12.8	110.1	4.70 (0.470)	2.07 (0.472)	21.13	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	All	6.4	54.4	4.00 (0.235)	0.94 (0.262)	64.84	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	All	8.8	79.3	4.37 (0.538)	1.59 (0.542)	34.09	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	All	17.5	67.9	4.22 (0.457)	1.46 (0.459)	38.52	21. 92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	All	18.2	89.6	4.50 (0.400)	1.45 (0.433)	38.98	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	All	NA	NA	NA	NA	NA	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	All	NA	NA	NA	NA	NA	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	All	5.7	65.0	4.17 (0.609)	1.72 (0.612)	29.74	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	All	NA	NA	NA	NA	NA	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	All	NA	NA	NA	NA	NA	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	All	4.4	119.4	4.78 (0.701)	2.46 (0.713)	14.29	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	All	13.0	173.4	5.16 (0.460)	2.99 (0.466)	8.36	6.21

Table 15. MAIC output: Progression-free survival outcomes – KM to 2.99 months followed by exponential (all covariates)

	Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (SE)			ESS	Adjusted mean	Adjusted ln(mean) (SE)	Δln(mean) (SE)	Updated	A11
NIVO+IPI												
CheckMate 142	NIVO+IPI	119										
FOLFOX												
CONFIRM2	Base case	429	5.47	1.70 (0.037)		All	18.6	51.1	3.93 (0.528)	2.23 (0.530)	6.82	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)		All	12.8	31.5	3.45 (0.401)	1.77 (0.403)	10.85	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)		All	6.4	27.3	3.31 (0.291)	1.41 (0.313)	15.63	7.00
FOLFIRI												
RAISE	Scenario	536	6.62	1.89 (0.046)		All	8.8	36.4	3.60 (0.446)	1.70 (0.448)	11.59	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)		All	17.5	28.3	3.34 (0.578)	1.43 (0.580)	15.30	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)		All	18.2	44.8	3.80 (0.517)	1.70 (0.531)	11.63	10.34
Trifluridine/tipiracil												
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)		All	NA	NA	NA	NA	NA	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)		All	NA	NA	NA	NA	NA	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)		All	5.7	43.2	3.77 (0.781)	2.38 (1.059)	5.89	3.35
Best supportive care												
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)		All	NA	NA	NA	NA	NA	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)		All	NA	NA	NA	NA	NA	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)		All	4.4	29.0	3.37 (0.495)	2.74 (0.544)	4.13	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)		All	13.0	51.9	3.95 (0.556)	3.27 (0.557)	2.43	1.58

Table 16. MAIC output: Progression-free survival outcomes – spline model (all covariates)

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (SE)		ESS	Adjusted mean	Adjusted ln(mean) (SE)	Δln(mean) (SE)	Updated	A11
NIVO+IPI											
CheckMate 142	NIVO+IPI	119									
FOLFOX											
CONFIRM2	Base case	429	5.47	1.70 (0.037)	All	18.6	77.2	4.35 (0.908)	2.65 (0.908)	3.81	5.94
NO16967	Scenario	314	5.36	1.68 (0.041)	All	12.8	38.8	3.66 (0.718)	1.98 (0.719)	7.41	5.45
CAPRI-GOIM	Scenario	79	6.70	1.90 (0.115)	All	6.4	78.4	4.36 (0.615)	2.46 (0.626)	4.59	7.00
FOLFIRI											
RAISE	Scenario	536	6.62	1.89 (0.046)	All	8.8	40.9	3.71 (0.653)	1.82 (0.655)	8.70	7.86
VELOUR	Base case	614	6.79	1.92 (0.047)	All	17.5	46.9	3.85 (0.778)	1.93 (0.780)	7.78	9.66
NCT01479465	Scenario	80	8.17	2.10 (0.121)	All	18.2	30.1	3.40 (0.647)	1.30 (0.658)	14.59	10.34
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	3.68	1.30 (0.112)	All	NA	NA	NA	NA	NA	4.29
RECOURSE/USA	Scenario	64	3.63	1.29 (0.193)	All	NA	NA	NA	NA	NA	3.38
TERRA	Scenario	271	3.99	1.38 (0.715)	All	5.7	121.1	4.80 (1.097)	3.41 (1.310)	1.77	3.35
Best supportive care											
RECOURSE/EUR	Base case	132	1.83	0.60 (0.032)	All	NA	NA	NA	NA	NA	2.14
RECOURSE/USA	Scenario	35	1.87	0.63 (0.093)	All	NA	NA	NA	NA	NA	1.67
LUMECOLON1	Scenario	382	1.88	0.63 (0.226)	All	4.4	34.5	3.54 (0.904)	2.91 (0.932)	2.93	2.12
TERRA	Scenario	135	1.97	0.68 (0.034)	All	13.0	118.7	4.78 (0.832)	4.10 (0.833)	0.89	1.58

Table 17. MAIC output: Overall survival outcomes – fully parametric log-logistic (all covariates)

Study characteristics					Adjustment set	Adjusted NIVO+IPI population			Relative treatment effect	Comparator mean survival outcomes	
Study	Scenario	N	Mean survival outcomes	ln(mean) (SE)		ESS	Adjusted mean	Adjusted ln(mean) (SE)	Δln(mean) (SE)	Updated	A11
NIVO+IPI											
CheckMate 142	NIVO+IPI	119									
FOLFOX											
CONFIRM2	Base case	429	17.32	2.85 (0.048)	All	18.6	122.1	4.81 (0.457)	1.95 (0.460)	20.04	14.52
NO16967	Scenario	314	13.96	2.64 (0.042)	All	12.8	88.0	4.48 (0.425)	1.84 (0.427)	22.42	13.50
CAPRI-GOIM	Scenario	79	21.18	3.05 (0.116)	All	6.4	46.8	3.84 (0.247)	0.79 (0.273)	64.03	21.80
FOLFIRI											
RAISE	Scenario	536	16.23	2.79 (0.065)	All	8.8	64.7	4.17 (0.544)	1.38 (0.548)	35.47	18.87
VELOUR	Base case	614	15.70	2.75 (0.046)	All	17.5	50.5	3.92 (0.434)	1.17 (0.437)	43.97	21. 92
NCT01479465	Scenario	80	20.97	3.04 (0.164)	All	18.2	94.4	4.55 (0.364)	1.50 (0.400)	31.40	41.40
Trifluridine/tipiracil											
RECOURSE/EUR	Base case	271	10.39	2.34 (0.086)	All	NA	NA	NA	NA	NA	15.41
RECOURSE/USA	Scenario	64	11.71	2.46 (0.231)	All	NA	NA	NA	NA	NA	12.05
TERRA	Scenario	271	11.60	2.45 (0.066)	All	5.7	49.1	3.89 (0.604)	1.44 (0.607)	33.37	8.48
Best supportive care											
RECOURSE/EUR	Base case	132	7.22	1.98 (0.199)	All	NA	NA	NA	NA	NA	10.77
RECOURSE/USA	Scenario	35	8.07	2.09 (0.483)	All	NA	NA	NA	NA	NA	7.31
LUMECOLON1	Scenario	382	10.24	2.33 (0.129)	All	4.4	93.1	4.53 (0.736)	2.21 (0.747)	15.55	9.47
TERRA	Scenario	135	8.70	2.16 (0.072)	All	13.0	129.0	4.86 (0.490)	2.70 (0.495)	9.53	6.21

Economic analysis

Table 18. Economic analysis: Additional MAIC analysis

Comparator	Study	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1				
Trifluridine-tipiracil	RECOURSE EUR	■	■	£13,388
BSC	RECOURSE EUR	■	■	£14,187
FOLFOX	CONFIRM2	■	■	£15,194
FOLFIRI	RAISE	■	■	£15,410
	VELOUR	■	■	£16,481
Scenario 2				
Trifluridine-tipiracil	RECOURSE EUR	■	■	£13,693
BSC	RECOURSE EUR	■	■	£14,444
FOLFOX	CONFIRM2	■	■	£15,327
FOLFIRI	RAISE	■	■	£15,741
	VELOUR	■	■	£16,712
Scenario 3				
Trifluridine-tipiracil	RECOURSE EUR	■	■	£14,005
BSC	RECOURSE EUR	■	■	£14,844
FOLFOX	CONFIRM2	■	■	£16,089
FOLFIRI	RAISE	■	■	£16,269
	VELOUR	■	■	£17,147
Scenario 4				
Trifluridine-tipiracil	RECOURSE EUR	■	■	£14,330
BSC	RECOURSE EUR	■	■	£15,118
FOLFOX	CONFIRM2	■	■	£16,231
FOLFIRI	RAISE	■	■	£16,625
	VELOUR	■	■	£17,390
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin				

Table 19. Economic analysis: Naïve unadjusted analysis

Comparator	Study	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Scenario 1				
Trifluridine-tipiracil	RECOURSE EUR	■	■	£13,247
BSC	RECOURSE EUR	■	■	£14,118
FOLFOX	CONFIRM2	■	■	£15,029
FOLFIRI	RAISE	■	■	£14,988
	VELOUR	■	■	£14,944
Scenario 2				
Trifluridine-tipiracil	RECOURSE EUR	■	■	£13,471
BSC	RECOURSE EUR	■	■	£14,335
FOLFOX	CONFIRM2	■	■	£15,267
FOLFIRI	RAISE	■	■	£15,224
	VELOUR	■	■	£15,179
Scenario 3				
Trifluridine-tipiracil	RECOURSE EUR	■	■	£13,843

BSC	RECOURSE EUR	▇		▇		£14,747
FOLFOX	CONFIRM2	▇		▇		£15,785
FOLFIRI	RAISE	▇		▇		£15,734
	VELOUR	▇		▇		£15,684
Scenario 4						
Trifluridine-tipiracil	RECOURSE EUR	▇		▇		£14,079
BSC	RECOURSE EUR	▇		▇		£14,976
FOLFOX	CONFIRM2	▇		▇		£16,039
FOLFIRI	RAISE	▇		▇		£15,985
	VELOUR	▇		▇		£15,934
BSC: best supportive care; FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin						

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3.   Bristol-Myers Squibb. Study CA209142: Ad hoc efficacy report. 2019.
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Patient organisation submission

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

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Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]
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1.Your name	▮▮▮▮▮▮
2. Name of organisation	Bowel Cancer UK
3. Job title or position	▮▮▮▮▮▮
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are the UK's leading bowel cancer charity. We are determined to save lives and improve the quality of life of everyone affected by bowel cancer by championing early diagnosis and access to best treatment and care. We support and fund targeted research, provide expert information and support to patients and their families, educate the public and professionals about the disease and campaign for early diagnosis and access to best treatment and care. The majority of our income is generated from individual, corporate and trust fundraisers. A small proportion (£78,048) is given by pharmaceutical companies in support of training for nurses and international activity in bowel cancer.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

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If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information we provide in this response on the experiences of patients was gathered from a survey of people diagnosed with advanced bowel cancer with high microsatellite instability or mismatch repair deficiency carried out by Bowel Cancer UK. We posted the survey on social media and our patient online forum for one week, and asked our Medical Advisory Board members to share it with relevant patients. Eleven patients responded to the survey in total. A handful of experiences are also shared from existing case studies gathered from patients diagnosed with advanced bowel cancer. The patients are a mixture of those being treated with immunotherapy - nivolumab with ipilimumab, nivolumab only and pembrolizumab, as well as patients who have broader experience of a range of treatments for their advanced bowel cancer.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of bowel cancer is life changing and can affect almost every aspect of daily life, not only for the individual diagnosed but also for their family and loved ones. This is even more acute for those diagnosed at the later stages of the disease, when we know it is harder to treat and the chance of survival is low. Patients experience numerous difficulties and challenges across the pathway, from initial diagnosis, to treatment, and care. In particular, these relate to the impact and reality of an advanced bowel cancer diagnosis, the difficulty and complexity in navigating treatment and care pathways and the impact treatment can have on quality of life.

Patients used words like 'devastating', 'tough', 'a battle', stressful' and 'difficult' to describe their overall experience living with advanced bowel cancer. Our community told us: |

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"It is extremely difficult, challenging, with pain on various levels; physical, emotional, psychological, and spiritual. It impacts work, relationships, social life."

"Living with cancer is both a physical and mental condition that requires support from professional experts and family to help one through the unknown and difficult journey ahead. It greatly affects your thought process and daily outlook on life leading to anxiety and depression."

"Difficult! So many treatments are aimed at other cancers instead of bowel cancer."

"Chemo was tough but in some ways it has been harder afterwards. During chemo I felt like something was being done to combat the cancer. I am back at work and struggling. Very tired. But trying to stay positive"

"Initially very stressful until I knew I was able to have immunotherapy treatment [Nivolumab]…..I did feel lots of dread as I didn't know how long I would be taking this [drug] as I knew it wouldn't really cure me. However, the past six months I have felt mentally stronger and felt physically well."

"There is a level of anxiety especially when scan or blood test results are due but this has diminished over time since the drug [Nivolumab with ipilimumab] has been shown to be working. Life is much more normal now than it was 12 months ago"

"Whilst using Nivolumab treatment it improved my quality of life with few side effects"

Patients undergoing treatments for advanced bowel cancer experience a range of side effects, which significantly affect their quality of life – both physically and emotionally.

Bowel Cancer UK has heard from a number of advanced bowel cancer patients who are experiencing painful side effects while going through treatment with cetuximab and panitumumab as first line treatment. Prolonged use of these drugs causes a number of skin toxicities and side effects including: Extremely painful red skin rashes and fissures; Dry and peeling skin across hands, feet and face; Cystic, painful acne-like spots; Severe paronychia; Loss of eye lashes and eye soreness; Nausea; Diarrhoea; Reduced appetite. Patients have also emphasised the psychological impact continued treatment has had. Many patients have described how their side effects have left them feeling debilitated, isolated and self-conscious.

"In December 2017, treatment was commenced with chemotherapy (FOLFIRI) and a biological targeted therapy - panitumumab. Despite a rocky start with severe side effects of diarrhoea, abdominal pains, fatigue, severe

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	neutropenia and skin rash, 6 cycles were completed with a dose titration. A CT scan concluded a phenomenal response with marked regression of multiple tumours in the liver."
	"I started treatment in October 2019. I had Folfox and Panitumumab….My skin was incredibly dry and despite the constant use of moisturiser, I was like a walking Head and Shoulders advert……I became incredibly sensible to extremes of temperature. I was tired, almost constantly exhausted.
	I was covered in spots, all over my scalp and face. It spread to my chest and back. I would wake up each morning with blood on my pillows and throughout my treatment it got worse. Some days I was literally peeling my face off my pillow…. As time progressed this got me more and more depressed. I know it is horrible but I had to comb through my beard trying to gently remove the dried blood and puss. It was painful and made me feel embarrassed.
	I also lost a lot of the feeling in my hands and feet, which still has yet to return….My memory has been badly affected. I struggle with names and lose track of what I have been saying, as well as struggle to concentrate."
	Unfortunately, often patients do not get access to the treatment and support to alleviate these side effects.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Survival rates for advanced bowel cancer are poor, with less than one in ten people surviving more than five years. These patients deserve access to the best quality treatment and care. For some patients these drugs can be lifesaving, while for others they can prolong life, resulting in more time to spend with loved ones. Therefore, it is essential patients gain timely access to the treatments that their clinicians feel could benefit them.
	However, current treatment options approved for use on the NHS for advanced bowel cancer are extremely limited. The impact of this on patients in terms of both survival and psychologically is detrimental, with many patients unable to access a treatment that could prolong their life and give them the best possible outcome. This also has financial implications for patients and their families, with many having to resort to fundraising or borrowing money in order to fund treatments privately. For patients and their families, this inequity of access causes unnecessary stress, worry and anxiety when they are already struggling to come to terms with being diagnosed advanced bowel cancer. Limiting access in this way means that patients may miss out on treatments that could extend their life.
	The majority of patients felt that treatment options available on the NHS were 'limited' or 'inadequate' for those with advanced bowel cancer, especially so for those with high microsatellite instability or mismatch repair deficiency. Our community told us:

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	"The bowel cancer with mismatch repair deficiency which I suffered meant only limited drugs were available to actively combat the disease as immunotherapy is not currently approved by NICE. I received chemotherapy treatment (Avastin) which unfortunately didn't work in my particular case in fact the cancer increased. I then received Nivolumab immunotherapy (the costs were covered by my medical provider). The improvement following the immunotherapy were apparent within a couple of months. The NHS Consultant and treatment team were very professional and caring. I feel I have been extremely lucky to benefit from immunotherapy treatment." *"My treatment (Nivolumab with ipilimumab) was fabulous however I feel treatment options for those with bowel cancer are limited and the most effective treatments need to be made more widely available."* *"Poor, colon cancer second biggest killer, early onset colorectal cancer rising rapidly, most current treatments are 20 to 30 years old, folfiri, folfox! And existing treatments don't seem to work very well."* *"Very limited. Early phase trials often only have a 5-10% chance or doing anything. Lack of scanners and leading edge technologies leaves UK trailing along way behind European countries"* *"Current treatments as in chemotherapy are barbaric! Tolerable but barbaric…..Us patients accept risk as the alternative is permanent for a very long time!"* *"Most other treatments were less effective and incurred more side effects."* Patient on Nivolimab *"They are inadequate for a whole patient population with lynch syndrome/ MSI high genetics"*
8. Is there an unmet need for patients with this condition?	Bowel Cancer UK argue there is an unmet need for this specific patient population and all of our responder's of the survey feedback a similar view. There are currently extremely limited treatment options available for people diagnosed with advanced bowel cancer with high microsatellite instability or mismatch repair deficiency. As such, patients described a range of issues across the pathway relating to diagnosis, treatment and care. *"Absolutely. Screening should start at 50, training should be given to GP's (mine was useless, and ignored my first appearance there in 10 years following a Bowel Cancer UK advert). Diagnostic equipment is lagging and new treatments/technologies are not available."* *"Yes particularly for those under fifty with symptoms. Also, the delay in treatment and referrals since covid."* *"Yes - for example 5% of metastatic cancer patients are MSI high but only a very small fraction of this number are offered immunotherapy with checkpoint inhibitors."*

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	"Bowel cancer is the poor relation compared to other cancers - these drugs need to be made available ASAP, and earlier in the treatment pathway"
	"This patient population have unique genetic profile which needs a personalised approach. These newer immunotherapy treatments are a lifesaver, yet are tragically unavailable on the NHS."
	"Yes the majority of NHS patients cannot afford to pay for this treatment, once a patient has had chemotherapy treatment and not had any beneficial response to it there doesn't seem to be any other treatment available."
	"I don't know anyone with my condition, or who is on immunotherapy, so whereas if it was breast cancer for example, there would be always someone I know who was in the same boat, so felt quite isolated in those terms."
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients have told us that immunotherapies and medicines that are personalised offer patients greater hope, treatment choice and means patients do not have to suffer the side effects of medicines unnecessarily that will not work for their particular genetic profile. Two patients in the survey did not respond to this question in the survey. The remaining ten patients raised the following advantages to this treatment: *"Having had surgery, 2 types of chemo and microwave ablation treatment as well as immunotherapy, I can say with confidence that the side effects of immunotherapy are dramatically less than any of the more traditional colorectal cancer treatments. Physically, immunotherapy has not given me abdominal pains, nausea, diarrhoea or fatigue in the same way that chemo did. In 15 months of treatment with immunotherapy I have not required any supplementary treatment to cope with side effects. I have been able to lead a normal life, to work full time and to play the same sports as I did before I had cancer. Mentally, I feel healthier than I have in a very long time and no longer feel the same daily pains and discomforts that used to make me worry that the treatment isn't working or that the cancer has returned"* Patient on nivolumab with ipilimumab *"I had no real side effects which is so much better than chemo and allows me to live life to the fullest."* Patient on Nivolumab with ipilimumab. *"Advantages: quicker intravenous applications, longer intervals between treatments, next to nothing in terms of side effects. I can work and interact with others as pretty much normal (unlike chemotherapy). Most importantly with regards to me....I live, and the disease is currently dormant!"* Patient on nivolumab with ipilimumab

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	"These treatments target the cancer differently, with some incredible results in comparison to the traditional chemotherapy that's routinely offered on the NHS. The side effects are less intrusive, and the treatment is administered in a considerably shorter time period. Chemo can be plugged in for over 48 hours, immunotherapy can be all done within an hour." *"I understand that the costs of Nivolumab are similar to other Chemotherapy drugs. I believe the benefits are shorter infusion times - 1hr compared to 6/7 hrs for standard chemotherapy enabling the hospital to treat more patients; Fewer side effects (my experience); Better quality of life and able to continue to work; Better outcome for patients - able to return to productive work and better life expectancy." Patient on Nivolumab* *"Nivolumab improved the quality of life for the period of time it lasted on me"* *"The huge benefit to the patients quality and extended life. The cost and time saving benefits for the NHS"* *"The body attacking the disease in the natural way and not via destructive chemo drugs"* *"PD-1 plus CTLA-4 works better with younger patients who have strong immune systems and very mutated cancers. Also those with genetic cancers such as Lynch syndrome and FAP."* *"These drugs are lifesaving and life enriching. I was a terminal patient, after a year of chemotherapy failed to control my cancer diagnosed in 2014. Because of my lynch syndrome/ MSI high, I was a good candidate for immunotherapy. The NHS rejected my individuals funding requested, and as a last resort I crowdfunded £200,000 for pembrolizumab (different, but works similar to the drug in question). I began pembro in June 2016 until May 2017. I have not had any treatment since, and I am 'No evidence of disease'. In December 2020, I will reach 6 years since my stage 4 bowel cancer diagnosis. This goes against the expectancy guides on the NHS. How many other people can have an enriched life with these new treatments? It's tragic that money, and lack of access, is the reason why this patient population die when incredible treatment is out there."*

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Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients raised disadvantages of the treatment, including the cost and lack of access for most people, as well as questions about its effectiveness and the fact there is some evidence of longer-term issues that can result from the treatment. Two patients in the survey did not respond to this question in the survey. The remaining ten expressed the disadvantages as follows :
	"The cost, and lack of access. Not enough doctors are aware of Lynch Syndrome, and how immunotherapy is targeted for this profile."
	"Some evidence of longer term issues e.g. adrenal gland issues, colitis."
	"The length of time it worked for me"
	"Very expensive. Still unpredictable in terms of the response. A few people have had hyper progression"
	"There will always be potential side-effects/toxicities, but these are less can be more condensed than chemo and much more tolerable in my experience."
	"I have not experienced any disadvantages - the immunotherapy eased my pain, successfully treated the cancer and enabled me to return to full time work."
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients described those who have bowel cancer with mismatch repair deficiency or similar, those newly diagnosed with the disease and younger people as groups that would benefit most from this treatment for the reasons outlined below.
	"MSI high patients will benefit disproportionately more as MSI high tumours have a higher level of mutational load which results in higher levels of immune activity at the tumour site and a greater likelihood of positive response to checkpoint inhibitor immunotherapy."
	"Lynch syndrome patients, and those cancers that have an MSI high profile. The treatment targets these cancers differently, by stimulating the T cells, to activate the immune system, which has overtime been unable to keep up with the cancer burden."

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	"These drugs and immuno-therapy trials should be offered to patients when first diagnosed - you would have healthier patients to treat - as opposed to the current system when you need to have tried all standard chemo before being offered a chance at immunotherapy, and when you are probably weaker, more advanced and with a worse prognosis." *"Younger people and those willing to change their lifestyle. For my 28 months on Keytruda (pembrolizumab) being vegan taking probiotics has helped."* *"MSI high patients like me. Other patient groups as per testing currently going on...In family hereditary disease suffers such as Lynch Syndrome patients and their children."*
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Three patients in the survey did not respond to this question in the survey. The remaining nine patients felt that equal access for these drugs was of upmost importance. *"Lack of equal access is a major issue with this treatment currently as only certain hospitals run clinical trials and some work more closely with manufacturers, such as BMS, than others. For the unlucky ones who do not have access to this treatment through the NHS there is a huge financial burden to be paid in order to access this treatment via the private sector"* *"Socio economic criteria aren't covered by the equality act, however the poorest in society won't be able to pay for these drugs privately"* *"They are available on the NHS for lung and skin cancers, but I had to spend my life savings and crowd fund to access my immunotherapy for colon cancer. Which seems to have worked!"* *"Without nivolumab I do not think I would still be here and filling in this questionnaire, all cancer patients should be treated equally and have access to any appropriate treatment."* *"No doctors ever suggested or recommended this course of treatment to me. I discovered it. I pursued it. I was extremely lucky to have the ability and drive in order to do this. That speaks of a huge inequality. Being one of a handful on this treatment for bowel cancer."*

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	"There is something truly remarkable about this treatment. I had no other options left and my tumors were growing. I began treatment 15 months ago and for 12 months now I have had no visible cancer and am able to live a normal life. My cancer was fast growing, not detectable and chemo resistant. There are many in my position who are deserving of an opportunity and it is right that if treatment is available it should be open to all who qualify on a fair and equitable basis."

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of bowel cancer can be life changing for those diagnosed, as well as their friends and family, and is even more acute for those at later stages of the disease when it is harder to treat and there is a low chance of survival.

- Current treatment options approved for use on the NHS for advanced bowel cancer are extremely limited with many patients unable to access a treatment that could prolong their life.

- Patients told us that immunotherapies and medicines that are personalised offer patients greater hope, treatment choice and means patients do not have to suffer the side effects of medicines that will not work for their genetic profile.

- Patients felt those who have bowel cancer with mismatch repair deficiency or similar, those newly diagnosed with the disease and younger people would benefit most from this treatment.

- All patients should have access to personalised, tailored treatment that is right for them. If outcomes for people with advanced bowel cancer are to improve, a one-size fits all approach to treating people with the disease will not work.

Thank you for your time.

Patient organisation submission
Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]
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Patient organisation submission
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Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

STA Report

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Rebecca Boffa	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Sarah Roberts	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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List of Abbreviations

AE	Adverse event
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicines Strategy Group
CADTH	Canadian Agency for Drugs and Technologies in Health
ESMO	European Society for Medical Oncology
PBAC	Pharmaceutical Benefits Advisory Committee
BICR	Blinded independent central review
IA	Investigator-assessed
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions;
SMC	Scottish Medicines Consortium
IHC	Immunohistochemistry
TRAE	Treatment-related adverse event
AESI	Adverse event of special interest
DBL	Database lock
DCR	Disease control rate
RWE	Real world evidence
AIC	Akaike Information Criteria
BIC	Bayesian Information Criteria
UK	United Kingdom
BSC	Best supportive care
CAPOX	capecitabine plus oxaliplatin
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
KM	Kaplan-Meier
CG	Clinical guidance
CI	Confidence interval
CIN	Chromosomal instability
CM142	CheckMate 142
CMS1	Consensus molecular subtype 1
CR	Complete response
CRC	Colorectal cancer
CS	Company submission
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
dMMR	DNA mismatch repair deficient
DOR	Duration of response
ESS	Effective sample size
DSU	Decision Support Unit

EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EGFR	Anti- epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ C-30	European Organization for Research and Treatment of Cancer QLQ-C-30
EQ-5D	EuroQol 5-dimensions
ERG	Evidence Review Group
FOLFIRI	Folinic acid, 5-fluorouracil, irinotecan
FOLFOX	Folinic acid, 5-fluorouracil, oxaliplatin
GI	Gastrointestinal
HrQoL	Health related Quality of Life
HTA	Health Technology Appraisal
ICER	Incremental Cost Effectiveness Ratio
IPD	Individual patient data
IRRC	Independent radiology review committee
ITC	Indirect treatment comparison
LYG	Life Years Gained
MAIC	Matching-adjusted indirect comparison
mCRC	Metastatic colorectal cancer
MMR	DNA mismatch repair
MSI	Microsatellite instability
MSI-H	Microsatellite instability high
MSI-L	Microsatellite instability low
MSS	Microsatellite stable
NA	Not applicable
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NIVO+IPI	Nivolumab plus ipilimumab
NR	Not reached
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PCR	Polymerase chain reaction
PD	Relapsed or progressed disease
PFS	Progression-free survival
PICOS	Population-Intervention-Comparators-Outcomes-Study
PSA	Probabalistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
pMMR	DNA mismatch repair proficient
PR	Partial response

PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	Relapse-free survival
SAE's	Serious Adverse Events
SD	Stable disease
SLR	Systematic literature review
STC	Simulated treatment cohort
TA	Technology Appraisal
TRI-TIP	Trifluridine-tipiracil
TTR	Time to recurrence
VAS	Visual analogue scale
VEGF	Anti-vascular endothelial growth factor
WTP	Willingness-to-pay

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1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 presents a summary of the ERG's key issues on the evidence submitted on the clinical and cost effectiveness of nivolumab with ipilimumab (NIVO+IPI) for previously treated metastatic colorectal cancer (mCRC) with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Comparisons between NIVO+IPI and comparators are all between single trial arms – unanchored comparisons	3.4
2	Treatment stopping rule	4.2.6.1.3 and 4.2.10.4
3	Survival extrapolations for NIVO+IPI (KM cut-off point in the semi-parametric models)	4.2.6.1
4	HSUVs according to progression status do not match the original source (CORRECT)	4.2.9
5	Treatment specific utilities	4.2.9
6	Subsequent therapy costs	4.2.10.4
7	ACM adjustments	4.2.7

Abbreviations: ACM, all-cause mortality; HSUV, health-state utility value; IPI, ipilimumab; KM, Kaplan Meier; NIVO, nivolumab

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are around the method used for indirect comparison, the KM cut-off point used to

inform the semi-parametric models for NIVO+IPI, the NIVO+IPI stopping rule and the health-state utility values (HSUVs).

1.2   Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression-free survival (PFS);
- Increasing overall survival (OS);
- Increasing the utility in patients on treatment above the utility in patients who receive current treatments.

Overall, the technology is modelled to affect costs by:

- Its higher acquisition cost than current treatments;
- Its higher incidence of AEs than current treatments.

The modelling assumptions that have the greatest effect on the ICER are:

- The treatment stopping rule for nivolumab.

1.3   Summary of the ERG's key issues

The ERG's key issues with the company's analyses are given in Table 2 to Table 8.

Table 2. Issue 1: Comparisons between NIVO+IPI and comparators are all between single trial arms – unanchored comparisons

Report section	3.4
Description of issue and why the ERG has identified it as important	No studies were identified that provide a direct comparison of NIVO+IPI versus any of the comparators of interest, and no network of trials could be connected in order to perform a network meta-analysis (NMA). The company has therefore performed unadjusted (naïve) and adjusted (unanchored MAICs) indirect comparisons to assess the relative efficacy of NIVO+IPI versus the comparators listed in the NICE final scope (CS, Appendix L).
	Naïve comparisons are assumed to be biased due to imbalances in observed and unobserved prognostic factors and effect modifiers between the study populations. In order to reduce this bias, the company performed MAICs adjusting either for a select set of covariates (partially adjusted, company's preferred option, CS Appendix L) or for all reported covariates (fully adjusted, clarification response A12).
	Irrespective of the analysis used (adjusted or unadjusted) there is an unquantifiable but likely very large amount of uncertainty around all the results presented, due to residual bias and differences between the studies that haven't or can't be adjusted for.
What alternative approach has the ERG suggested?	The company has explored a comprehensive range of analyses comparing the single trial arms of NIVO+IPI and the comparators of interest.
	Of the different adjusted analyses presented by the company, the ERG considers the MAIC adjusted for all available covariates to provide the most accurate results, although the imprecision is very large, and the results are unstable. The ERG's preferred approach is therefore the use of a naïve comparison as it is transparent in terms of the likely biases that exist within the comparison and the analysis itself has not introduced additional bias into the comparison.
What is the expected effect on the cost-effectiveness estimates?	Cost-effectiveness results are robust to alternative sources of comparator data and alternative analysis methods (naïve, partially or fully adjusted). The only method that led to noteworthy increases in the ICER was the fully adjusted set (using all available covariates). Even so, this analysis increased the ICER to a maximum of £17,149 (versus FOLFIRI based on VELOUR). Whatever the analysis there is unquantifiable bias that will affect the certainty of the clinical and cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	The main uncertainties of the unanchored comparisons are likely to be resolved by the reporting of the phase III RCT CheckMate 8HW, which will provide comparative efficacy of NIVO+IPI versus the current standard of care in patients with MSI-H/dMMR mCRC who have received at least one prior line of systemic therapy. Preliminary results for this RCT are currently expected in ▮▮▮▮

Abbreviations: CS, company submission; dMMR, mismatch repair deficiency; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; KM, Kaplan Meier; MAIC, matching adjusted indirect comparison; MSI-H, high microsatellite instability; NIVO, nivolumab; QALY, quality-adjusted life year; RCT, randomised controlled trial

Table 3. Issue 2: Treatment stopping rule

Report section	4.2.6.1.2 and 4.2.10.4
Description of issue and why the ERG has identified it as important	The ERG considers that the 2-year stopping rule should be removed from the economic analysis as no formal stopping rule was applied during CheckMate 142. During CheckMate 142, around ▇ of patients were still on nivolumab treatment at 2 years. The ERG's clinical experts also fed back that their preference would be to continue nivolumab treatment until disease progression and not to take patients off nivolumab treatment if they are still deriving a benefit and remain progression-free at 2 years. What's more, the committee for TA439 concluded that it was inappropriate to implement a stopping rule in people with mCRC.
	The ERG also notes that the nivolumab stopping rule in the model also prevents patients who discontinue nivolumab at month 24 from incurring subsequent therapy costs. The ERG considers this to be counterintuitive to the company's base case assumption that patients begin subsequent therapy upon discontinuation. As a minimum, patients who have progressed and discontinued nivolumab should incur subsequent therapy costs.
What alternative approach has the ERG suggested?	The ERG considers that removing the 2-year stopping rule is a more appropriate reflection of how NIVO+IPI will be used in UK clinical practice and better reflects the clinical benefits observed in CheckMate 142.
	Removing the stopping rule also removes the issue with the logic of the model that patients who discontinue nivolumab at the point of the stopping rule do not incur subsequent therapy costs.
What is the expected effect on the cost-effectiveness estimates?	As shown in Section 5.1.2.6, removing the 2-year stopping rule increases the ICER for NIVO+IPI above £30,000 per QALY in each comparison.
What additional evidence or analyses might help to resolve this key issue?	Evidence in support of a 2-year stopping rule is currently being derived in the form of CheckMate 8HW, where a stopping rule was included in the protocol, and in CheckMate 142, where a protocol amendment in Feb 2019 included as an optional stopping point. Preliminary results for CheckMate 8HW are currently expected in ▇▇▇

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; mCRC, metastatic colorectal cancer; NIVO, nivolumab; QALY, quality-adjusted life year

Table 4. Issue 3: Survival extrapolations for NIVO+IPI (KM cut-off point in the semi-parametric models)

Report section	4.2.6.1
Description of issue and why the ERG has identified it as important	In order to model PFS, ToT and OS for NIVO+IPI, the company applied 6.44 months of KM data followed by a parametric extrapolation. The ERG is concerned that using 6.44 months of KM data to inform the semi-parametric extrapolation unnecessarily cuts the amount of data that can be used to inform the long-term extrapolation.
What alternative approach has the ERG suggested?	Based on feedback from the ERG's clinical experts and visual inspection of the KM curves, cumulative hazard plots and diagnostic plots, the effect of NIVO+IPI starts to become apparent at around ███████████████████, as indicated by the company. At the clarification stage the company was therefore asked to consider alternative approaches to extrapolate PFS, ToT and OS. For PFS and ToT, this included a semi-parametric model with KM data up to 3 months and a spline-based model. For OS, this included a semi-parametric model with KM data up to 3 months and a fully parametric model as a similar dramatic change in hazard is not seen in the OS curve as it is for PFS curve. As explained in Section 4.2.6, the ERG considers the semi-parametric models, with KM data up to 2.99 months, the most appropriate for PFS, ToT and OS and employs these models in its base case analyses. The key reason for choosing these models is because they represent the ██████████████ well and extend the amount of data that can be used to inform the long-term extrapolation. The spline-based model for PFS and the fully parametric model for OS could also be disregarded due to their poorer fit statistics.
What is the expected effect on the cost-effectiveness estimates?	Using semi-parametric models with KM data up to 2.99 months has a small impact on the cost-effectiveness results. Based on the unadjusted analysis (naïve comparison), the ICERs for NIVO+IPI reduced compared to the company's base case analyses and ranged from £13,250 (versus TRI-TIP) to £14,939 (versus FOLFOX) (see Table 50). Based on the MAIC which adjusts for all available covariates, the ICER for NIVO+IPI increased to a maximum of £18,255 (versus FOLFIRI using VELOUR). (see Table 46).
What additional evidence or analyses might help to resolve this key issue?	As noted above, the ERG proposes alternative approaches to extrapolate PFS, ToT and OS. The ERG also sought clinical expert advice on the plausibility of these curves. They advised the ERG that long-term projections are impossible to predict and that all curves are clinically plausible. The ERG also notes that a considerably longer follow-up period would be necessary (potentially 10 years or above) to validate the curves generated from CheckMate 142.

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; KM, Kaplan Meier; MAIC, matching adjusted indirect comparison; NIVO, nivolumab; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; SP, semi-parametric (piecewise); ToT, time on treatment

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Table 5. Issue 4: HSUVs according to progression status do not match the original source (CORRECT)

Report section	4.2.9
Description of issue and why the ERG has identified it as important	During the factually accuracy check, the company explained that the HSUVs applied in the economic analyses were taken from TA242 and not the CORRECT publication. The pre-progression HSUV between the two sources is similar (0.74 vs 0.75, CORRECT and TA242, respectively), but there is a large difference in the post-progression HSUV (0.59 vs 0.69, CORRECT and TA242, respectively). The values identified by the ERG in the CORRECT publication were used and accepted in TA405. The ERG for TA242 was also concerned that the post-progression HSUV (0.69) was too high. As such, the ERG is unclear why TA242 was chosen to inform the HSUVs in the company's base case analyses. Given that patients in the NIVO+IPI arm stay in the post-progression health state for a substantially longer amount of time than patients in the comparator arms, using a higher post-progression utility value biases the results in favour of NIVO+IPI.
What alternative approach has the ERG suggested?	Applying the utility values reported in the CORRECT publication that were also used and accepted in TA405.
What is the expected effect on the cost-effectiveness estimates?	As shown in the ERG's scenario analyses (see Table 47), applying the utility values reported in the CORRECT publication that were also used and accepted in TA405, increases the ICER for NIVO+IPI by around £2,000 per QALY in each comparison.
What additional evidence or analyses might help to resolve this key issue?	The company needs to justify why the HSUVs in TA242 were preferred to those in CORRECT and TA405. Clinical expert opinion would also be useful to help determine the appropriate post-progression HSUV (0.59 or 0.69).

Abbreviations: ERG, Evidence Review Group; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NIVO, nivolumab; QALY, quality-adjusted life year.

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Table 6. Issue 5: Treatment specific utilities

Report section	4.2.9
Description of issue and why the ERG has identified it as important	The ERG has several concerns around the appropriateness of the on-treatment utility value for NIVO+IPI: • The on-treatment utility value for NIVO+IPI was derived from patients in CheckMate 142 (▉▉▉) and this is comparable to the utility value associated with the general population (0.842). Clinical expects advised the ERG that they would expect someone receiving second line treatment for mCRC to have a lower QoL than the general population. • Utility values in the comparator arm were derived from the CORRECT study[1] and the pre-progression utility value from CORRECT is considerably lower than the on-treatment utility value derived from patients in CheckMate 142 (0.75 vs ▉▉▉). Clinical experts advised the ERG that they would not expect a significant difference in the HSUVs between treatments and concluded that a novel mechanism of action alone was insufficient to warrant treatment-specific utility values. • Following a clarification request, the company compared the baseline characteristics in CORRECT with the baseline characteristics in CheckMate 142 and highlighted important differences. Although it is difficult to predict the impact of these different characteristics on QoL, the ERG is cautious about combining utility values from CheckMate 142 and CORRECT in the same analysis and would prefer one source for consistency.
What alternative approach has the ERG suggested?	The ERG considers using utility values according to progression status, from one study, to be more appropriate.
What is the expected effect on the cost-effectiveness estimates?	Using the CORRECT utility values to inform the NIVO+IPI arm (NIVO+IPI utility values were assumed as per comparators and applied by progression status, as opposed to treatment status) has a minimal impact on the cost-effectiveness estimates (see Table 45). This is because patients in the NIVO+IPI arm spend a shorter amount of time on the high on-treatment utility value (▉▉▉) and a longer amount of time on the pre-progression utility value (0.75).
What additional evidence or analyses might help to resolve this key issue?	A randomised controlled trial with an appropriate comparator arm that collects EQ-5D data.

Abbreviations: ERG, Evidence Review Group; ECOG, Eastern Cooperative Oncology Group; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; mCRC, metastatic colorectal cancer; NIVO, nivolumab; PFS, progression free survival; QALY, quality-adjusted life year; QoL, quality of life

Table 7. Issue 6: Subsequent therapy costs

Report section	4.2.10.4
Description of issue and why the ERG has identified it as important	The company applied the same one-off subsequent therapy cost (£1,621.21) to all treatment arms. As the treatment arms have different survival times, the ERG considers this to be an unreasonable simplification and in favour of NIVO+IPI as this treatment is associated with prolonged survival.
What alternative approach has the ERG suggested?	In response to a clarification request, the company provided a scenario where the one-off subsequent therapy cost is applied as a weekly cost (£69.99). Although this is one step closer to accounting for differences in survival, the composition (and weekly cost) could change over time. As such, the composition and duration of subsequent therapies would benefit from further exploration by the company.
What is the expected effect on the cost-effectiveness estimates?	As shown in Section 6.3, applying a weekly subsequent therapy cost (£69.99) increases the ICER for NIVO+IPI by around £5,000 per QALY in each comparison.
What additional evidence or analyses might help to resolve this key issue?	During the clarification stage the company noted that since the publication of TA405, no new CRC therapies have been appraised by NICE and there has been no major practise-changing research published. As such, the ERG considers that the company should elicit clinical expert opinion using the SHELF methodology to obtain aggregate judgements on the subsequent therapy regimens that are likely after NIVO+IPI and each comparator. The company could also assess the subsequent cancer therapies from CheckMate 142 at the updated data cut (Oct 2020) and make inferences from that data for NIVO+IPI.

Abbreviations: CRC, colorectal cancer; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; NICE, National Institute for Health and Care Excellence; NIVO, nivolumab; QALY, quality-adjusted life year; SHELF, Sheffield Elicitation Framework

Table 8. Issue 7: ACM adjustments

Report section	4.2.7
Description of issue and why the ERG has identified it as important	The company included ACM in addition to the disease-related mortality by multiplying the survival functions. Without this adjustment, the probability of survival is higher for patients in the NIVO+IPI arm with mCRC than the general population from year 32 (i.e. the ACM curve crosses the disease-specific OS curve). The ERG and its clinical expert agree with the company that a statistical cure model is inappropriate. As such, excess mortality from the disease needs to be modelled.
What alternative approach has the ERG suggested?	According to NICE DSU TSD 21, the company could explore an excess mortality model and isolate the cause-specific mortality by partitioning the ACM into that due to other causes and the excess mortality caused by the disease of interest. This approach was suggested to the company during the clarification stage but was not acknowledged in their response to clarification.
What is the expected effect on the cost-effectiveness estimates?	The ERG is unable to suggest what impact an excess mortality model would have on the results. It is possible that the results will be consistent with those reflected in the CS.
What additional evidence or analyses might help to resolve this key issue?	As requested at the clarification stage, the company may provide an excess mortality model.

Abbreviations: ACM, all-cause mortality; DSU, Decision Support Unit; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; mCRC, metastatic colorectal cancer; NICE, National Institute for Health and Care Excellence; NIVO, nivolumab; OS, overall survival; TSD, Technical Support Document

1.4 Summary of ERG's preferred assumptions and resulting ICER

Table 9 summarises the ERG's preferred assumptions and the cumulative impact these assumptions have on the ICER. Table 10 changes each assumption from the company's base case individually. Only one comparator (FOLFOX) is provided in Table 10 given that the magnitude of each change is similar for each comparator. Fully incremental results are provided in

Table 11. The ERG could not produce probabilistic sensitivity analysis (PSA) ICERs for its base case as the PSA takes several hours to run and due to paucity of time and complexity of the model, some scenarios could not be integrated with the PSA. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.3.

Table 9. Summary of ERG's preferred assumptions and resulting ICER (cumulative impact)

Preferred assumption	Section in ERG report	Cumulative ICER (£/QALY) NIVO+IPI vs			
		TRI-TIP	BSC	FOLFOX	FOLFIRI
Unadjusted analysis (naïve comparison)	3.4 and 4.2.6.2.1	13,304	14,177	15,056	14,933

Assumption	Section	NIVO+IPI	FOLFOX	Inc.	ICER
SP extrapolation of NIVO+IPI PFS using 2.99 months of KM data	4.2.6.1.4	13,445	14,314	15,206	15,141
SP extrapolation of NIVO+IPI ToT using 2.99 months of KM data	4.2.6.1.4	13,303	14,176	15,055	14,992
SP extrapolation of NIVO+IPI OS using 2.99 months of KM data	4.2.6.1.4	13,250	14,121	14,989	14,927
No stopping rule	4.2.6.1.4	34,326	34,552	37,257	36,915
ACM adjustment to ToT	4.2.7	32,456	32,735	35,290	34,970
HSUVs by progression status using the CORRECT values in TA405[2]	4.2.9	37,399	37,637	40,736	40,457
Additional monitoring for NIVO+IPI to reflect the SmPC	4.2.10.2	37,625	37,856	40,976	40,695

Abbreviations: ACM, all-cause mortality; BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; KM, Kaplan Meier; NIVO: nivolumab; OS, overall survival; PFS, progression free survival; SmPC, summary of product characteristics; SP, semi-parametric; ToT, time on treatment; TRI-TIP, trifluridine-tipiracil

Table 10. ERG's results using its preferred assumptions (individual impact vs FOLFOX)

Results per patient	NIVO+IPI	FOLFOX	Incremental value
Company base case			
Total costs (£)	■	12,176	■
QALYs	■	0.884	■
ICER (£/QALY)			14,839
Unadjusted analysis (naive comparison)			
Total costs (£)	■	12,334	■
QALYs	■	0.975	■
ICER (£/QALY)			15,056
SP extrapolation of NIVO+IPI PFS using 2.99 months of KM data			

Total costs (£)	▮	12,176	▮
QALYs	▮	0.884	▮
ICER (£/QALY)			14,987
SP extrapolation of NIVO+IPI ToT using 2.99 months of KM data			
Total costs (£)	▮	12,176	▮
QALYs	▮	0.884	▮
ICER (£/QALY)			14,690
SP extrapolation of NIVO+IPI OS using 2.99 months of KM data			
Total costs (£)	▮	12,176	▮
QALYs	▮	0.884	▮
ICER (£/QALY)			14,777
No stopping rule			
Total costs (£)	▮	12,176	▮
QALYs	▮	0.884	▮
ICER (£/QALY)			33,814
HSUVs by progression status using the CORRECT values in TA405 (PFS 0.74 and PD 0.59)			
Total costs (£)	▮	12,176	▮
QALYs	▮	0.792	▮
ICER (£/QALY)			15,810
Additional monitoring for NIVO+IPI to reflect the SmPC			
Total costs (£)	▮	12,176	▮
QALYs	▮	0.884	▮
ICER (£/QALY)			14,974

Abbreviations: ACM, all-cause mortality; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; KM, Kaplan Meier; NIVO: nivolumab; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; SmPC, summary of product characteristics; SP, semi-parametric; ToT, time on treatment

Table 11. ERG's base case results, fully incremental

Technologies	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
BSC	£9,303	0.376	-	-	-
FOLFIRI	£11,525	0.822	██████	████	£4,982
FOLFOX	£12,334	0.877	████	████	£14,709
NIVO+IPI	████	████	██████	████	£40,976

Note: TRI-TIP dominated by FOLFOX (FOLFOX less expensive and more effective than TRI-TIP)

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

2 Introduction and background

2.1 Introduction

This report provides a critique of the evidence submitted by Bristol Myers Squibb to the Single Technology Appraisal (STA) in support of the clinical and cost effectiveness of nivolumab (Opdivo®) plus ipilimumab (Yervoy®), hereafter referred to as NIVO+IPI, as a regimen for adults with metastatic colorectal cancer (mCRC) with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR).

2.2 Background

Within the company submission (CS), the company provides an overview of NIVO+IPI, including their mode of action, dose and method of administration (Section B.1.2). Direct evidence submitted in support of the clinical effectiveness of NIVO+IPI in the population of interest to this STA is derived from one non-randomised single arm phase II clinical trial, CheckMate 142.[3]

Within Section B.1.3 of the CS, the company provides an overview of mCRC with MSI-H or dMMR, including prevalence, prognosis, staging and disease management. Based on advice from its clinical experts, the Evidence Review Group (ERG) considers the CS to present an accurate overview of the aetiology and diagnosis of mCRC that is MSI-H or dMMR. To aid understanding of some points raised in the ERG's critique of the submitted evidence in the context of the decision problem, the ERG provides a summary of the management of mCRC in current UK practice as well as aspects of mCRC not covered in detail in the CS and that potentially affect response to treatment and prognosis, including how presence of MSI-H or dMMR impacts on course of disease.

2.2.1 Metastatic colorectal cancer

Colorectal cancer (also known as bowel cancer) starts in either the colon or the rectum. Stage of disease at presentation is the strongest prognostic factor for clinical outcomes in CRC, with metastatic disease being associated with the poorest survival.[4] Metastatic CRC refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer often first spreads to the liver, but metastases may also occur in other parts of the body including in distant lymph nodes, peritoneum, and more rarely in bones or the brain. Primary tumour position, in terms of left or right side, can impact on disease progression, overall survival (OS) and response to treatment; compared with tumours on the left, tumours on the right are more likely to be at an advanced stage of disease at presentation and, therefore, have a poorer prognosis. Additionally, right and left tumours differ in their molecular characteristics and histology. Deficits in the MMR

pathway are more commonly identified in tumours located on the right of the colon or rectum, whereas those on the left typically have more anomalies in genes involved in chromosomal instability, such as KRAS and p53. Positioning of tumour is reported to influence response to treatment,[5] with left-sided CRC tumours tending to show better response to adjuvant chemotherapy (e.g., 5-fluorouracil-based treatment) and to targeted therapy (e.g., inhibitors of epidermal growth factor receptor [EGFR]). By contrast, right-sided CRCs do not respond well to conventional chemotherapies, and are reported to have better outcomes with immunotherapies.[5] Various other patient characteristics can influence response to treatment and the course of the disease, including age, ethnicity, the size of metastases and ECOG status.[5]

Colorectal cancer is thus a heterogenous disease. Although disease stage remains the key determinant of prognosis, there is variability in clinical outcomes for the same disease stage.[6, 7] Various genetic anomalies have been identified as having a role in development of CRC, with differences in mutations across patients likely contributing to heterogeneity in clinical outcomes. This is discussed in more detail in the following Section 2.2.2.

2.2.2 Microsatellite instability, mismatch repair, and other genetic anomalies involved in development and prognosis of colorectal cancer

Two molecular pathways involved in CRC are the MSI and the chromosomal instability (CIN) pathways.[5-7] Most CRCs develop via the CIN pathway, whereas 12–15% arise from the MSI pathway that is, in turn, a consequence of dMMR.[6, 7] Genomic stability is maintained through the DNA MMR system, which repairs errors in insertions, deletions, and base–base mismatches introduced into microsatellites during DNA replication and combination.[6, 7] Microsatellites are short, tandemly-repeated sequences (1–6 base pairs) occurring throughout the genome. As a result of their repeated structure, microsatellites are prone to mutation. Presence of microsatellites with a sequence not occurring in germline DNA indicates presence of MSI and a dMMR system, and, therefore, microsatellites are a marker of dMMR.[6, 7] The DNA MMR system comprises four MMR genes and their encoded proteins (MLH1, MSH2, MSH6, PMS2).[6, 7] Inactivation of MLH1 and MSH2 accounts for over 90% of dMMR CRCs due to either mutation or more frequently due to loss of gene expression due to promoter methylation of hMLH-1. Deficiency of MMR results in the production of a truncated, non-functional protein or the loss of a protein, which causes MSI. Therefore, dMMR is frequently assessed by testing for loss of an MMR protein with immunohistochemistry or for MSI using a polymerase chain reaction (PCR)-based assay. The ERG's clinical experts commented that, generally, immunohistochemistry assessment of MMR proteins is more commonly conducted in UK pathology laboratories than PCR testing of MSI. While the ERG's clinical experts noted that PCR

testing is more complex, they agreed that diagnostic results are broadly similar across the two techniques.

Tumours arising from a dMMR pathway often have distinct features, such as origin in the right side of the colon or rectum and poorly differentiated morphology often with an intense lymphoid infiltrate.[8, 9] In early-stage CRC, dMMR tumours are associated with a favourable prognosis.[9] Prevalence of dMMR is low in mCRC (3.5%), which supports the proposal that dMMR tumours have a lower potential to metastasise. Once the disease is at the metastatic stage, the implications of dMMR on patient prognosis remains somewhat uncertain. Some evidence, including that from several large-scale studies, suggests that when dMMR tumours are present in mCRC, they are associated with a considerably worse outcome than those with a functional MMR system.[9-21] Evidence is nevertheless mixed, with some studies concluding that there is no prognostic difference between MSI-H and microsatellite stable patients.[22, 23] Furthermore, most evidence is based on first-line mCRC patients rather than those who have been previously treated; there is thus currently no evidence on the impact of MMR/MSI status on outcomes in the population of interest for this appraisal. Nonetheless the ERG's clinical experts, along with the company's own experts, advised that this patient group often appear to have worse survival outcomes in clinical practice.

Other genetic anomalies involved in pathways leading to the development of CRC, and that are now targets for treatment, are those affecting proteins acting in the Ras-Raf-mitogen-activated protein kinase (MAPK) signalling pathway.[24] One such gene is BRAF, which is a modulator of the MAPK signalling pathway. BRAF mutations are present in 10% of CRC, and tumours with BRAF mutations exhibit discrete clinical characteristics and outcomes. A specific mutation, BRAF^{v600E}, accounts for approximately 90% of all BRAF mutations seen in CRC. Additionally, BRAF^{v600E} is strongly associated with MSI. Clinical experts advising the ERG estimated that a BRAF mutation is seen in approximately a third of mCRC dMMR/MSI-H tumours. People with BRAF mutant CRC have low response rates to conventional therapies and poor OS. An analysis of individual patient data (IPD) from four RCTs evaluating first-line treatment in mCRC found that median PFS and OS were significantly worse for those with BRAF mutation (includes both dMMR and MMR) compared with those with BRAF wild-type.[9]

Other genes involved in the MAPK signalling pathway are the RAS genes, KRAS and NRAS.[24] Mutations in KRAS and NRAS are present in 50% of CRCs.[25] KRAS/NRAS mutations lead to activation of the MAPK signalling pathway downstream of EGFR, rendering these tumours resistant to anti-EGFR therapies, such as cetuximab and panitumumab.[26]

2.2.3   Treatment pathway for metastatic colorectal cancer

Treatments for mCRC aim to prolong survival and improve quality of life. The main treatment options for mCRC include surgery (to resect the primary tumour or metastases) and chemotherapy. There are currently no specific treatments available for mCRC with dMMR/MSI-H; thus the treatment pathway for this subgroup of patients does not differ from mCRC patients in general. The main first- and second-line chemotherapy regimens for mCRC recommended by the National Institute for Health and Care Excellence (NICE) are 5-fluorouracil (5-FU) or capecitabine based combination therapies, including: FOLFOX (5-FU, oxaliplatin and folinic acid), FOLFIRI (5-FU, folinic acid and irinotecan) and CAPOX (capecitabine and oxaliplatin).[27] Targeted biologic treatments, such as the anti-EGFR treatments, cetuximab and panitumumab, are also recommended for first-line treatment of RAS wild-type mCRC.[27] The clinical experts advising the ERG noted that it is uncommon for mCRC patients to receive single agent therapy, such as capecitabine, raltitrexed or irinotecan.

Choice of treatment at each subsequent line of therapy is based on the previous treatment received, with the general pathway being that each patient receives each combination of chemotherapy available throughout subsequent treatment lines. For example, patients receiving FOLFIRI may receive FOLFOX at second line. However, post-second line treatment options are currently limited in the UK, with trifluridine-tipiracil being the main treatment at this stage. Best supportive care (BSC) is reserved for patients not fit enough for further treatment, although the clinical experts advising the ERG noted that each line of chemotherapy may include some elements of BSC as required by each patient, with the amount of supportive care required increasing as patients progress throughout lines of treatment. The ERG's clinical experts further noted that response to treatment typically reduces at each line of treatment, and that the number of patients fit for a subsequent line of treatment reduces considerably at each treatment line.

2.3   Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by the NICE, together with their rationale for any deviation from the final scope (Table 12).[28] The key differences between the decision problem addressed in the CS and the scope are discussed in greater detail in the sections that follow.

Table 12. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population	Adults with previously treated recurrent or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.	███████████████████████████████ ███████████████████████████████ ████████████████████	The wording has been updated to reflect the proposed ████████ ███████████, in line with the NICE reference case.	The population in CheckMate 142 (the key trial informing the submission) is in line with the population in the final scope issued by NICE. However, this trial is a single-arm study and data from other studies was used to inform the comparators of interest. The company did not identify any comparator studies in the relevant population (mCRC with dMMR/MSI-H) and instead relied on comparator studies of the overall mCRC population (see sections 0 and 3.4 for further details).
Intervention	Nivolumab with ipilimumab.	Nivolumab with ipilimumab.	NA	The intervention in the CheckMate 142 is NIVO+IPI, as specified in the final scope issued by NICE. Although the ERG notes a difference in the

				expected MA dosage compared with the dosage used in CheckMate 142, and that the company has applied a 2 year stopping rule for NIVO+IPI in the economic model which was not used in the trial or specified in the expected MA (see Section 2.3.2 for details)
Comparator(s)	For people having second- or subsequent-line treatment: • Single-agent irinotecan (after FOLFOX) • FOLFIRI (after either FOLFOX or CAPOX) • FOLFOX (after either FOLFIRI or CAPOX) • Raltitrexed (if 5-fluorouracil and folinic acid are not suitable) • Trifluridine-tipiracil • Best supportive care (BSC)	For people having second- or subsequent-line treatment: • Trifluridine-tipiracil • FOLFOX • FOLFIRI • BSC. Note: given the limited use of raltitrexed and single-agent irinotecan in UK clinical practice, we do not believe these comparisons should inform decision making. However, cost-effectiveness assessments versus these comparators has been provided for completeness with the final scope.	Following clinical validation[29], the key comparators in a previously treated MSI-H mCRC population were highlighted as being: • FOLFOX/FOLFIRI (both used interchangeably, primarily in 2L. Estimated 40% patients each). • Trifluridine-tipiracil (mainly used in 3L and beyond, once other options are exhausted, including clinical trial enrolment). Estimated 5–10% of patients. • BSC (mainly used in later lines). Usually the last treatment option for patients who cannot tolerate active	All comparators in the final scope are included in the submission. The ERG agrees with the company's view on the most relevant comparators.

| | | | treatment. Estimated 6% of patients.

Clinical expert opinion confirmed that both single agent irinotecan and raltitrexed are rarely used in clinical practice (<5% patients combined), and mainly in patients where other treatments are contraindicated. | |
|---|---|---|---|---|
| Outcomes | The outcome measures to be considered include:

• overall survival

• progression-free survival

• response rates

• adverse effects of treatment

• health-related quality of life. | As per the scope, with the following specifics:

• progression-free survival (BICR-assessed, investigator-assessed)

• response rates (investigator-assessed ORR, BICR-assessed ORR, duration of response). | Efficacy outcomes have been presented to be in line with those reported in the CM142 study. | All outcomes outlined in the scope reported, however data for primarily OS are immature. |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. | Adhering to the reference case:

• the cost-effectiveness is expressed in terms of an incremental cost per quality-adjusted life year (QALY).

• A lifetime horizon is used. | As noted in the final scope, current NICE guidance recommends that all people with colorectal cancer should be offered testing when first diagnosed, using immunohistochemistry for mismatch repair proteins or MSI | Based on advice from the ERG's clinical experts, the company's rationale to exclude testing costs is considered reasonable by the ERG, as assessment of MSI or dMMR is standard clinical practice |

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The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Costs will be considered from an NHS and Personal Social Services perspective.

The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The economic modelling should include the costs associated with diagnostic testing for microsatellite instability status in people with metastatic colorectal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the

- the economic analyses has been conducted from an NHS and Personal Social Services perspective.

- the Patient Access Scheme (PAS) has been applied in economic analyses for all BMS products.

The economic modelling does not include costs associated with diagnostic testing for microsatellite instability status in people with metastatic colorectal cancer who would not otherwise have been tested.

testing to identify tumours with dMMR.[30, 31] This was based on economic evaluations conducted as part of Diagnostics Guidance 27 [DG27].[31] Further, NG151 notes that testing for dMMR may inform systemic therapy choices for those with non-metastatic colorectal cancer, but the NICE diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer already recommends such testing for all people with colorectal cancer when first diagnosed.[32] For this reason no further recommendations were made about testing for deficient DNA mismatch repair.

This assumption is validated by clinical experts, who note that this is an easy test to carry out and that all patients should be tested given it is in the NICE guidance. In particular, given that immuno-oncology therapies are available for this group, testing for this MSI high status is even more important.[29]

for all patients with mCRC.

| | Guide to the Methods of Technology Appraisals. | | Further, this is in line with ERG comments on an ongoing mCRC appraisal (ID1598), where it was noted that testing for *BRAF* status is "recommended in the updated NICE guideline (NG151) for all patients with mCRC at first diagnosis to help guiding the selection of systemic anti-cancer therapy. Consequently, the test is becoming a standard care and does not present an incremental cost compared with comparators for the use of the technology."[32]

In summary, as per NICE guidance, all patients should now be tested across the UK.[31] Therefore, we believe that the appropriate economic analysis for this STA should be that of NIVO+IPI itself, excluding diagnostic test costs. | |
| Special considerations, including issues related | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does | No equality issues have been identified or are anticipated. | NA | - |

to equity or equality	not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			

Abbreviations: BICR, blinded independent central review; BSC, best supportive care; CAPOX; capecitabine plus oxaliplatin; dMMR, mismatched repair deficiency; ERG, Evidence Review Group; FOLFIRI; folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; MAIC, matching adjusted indirect comparison; mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability; MMR, mismatched repair; NA, not applicable; NICE, National Institute for Health and Care Excellence; NIVO+IPI, nivolumab plus ipilimumab; ORR, objective response rate; OS, overall survival; PAS, patient access scheme; QALY, Quality Adjusted Life Year; STA, single technology appraisal.

2.3.1   Population

The key trial assessing NIVO+IPI is CheckMate 142, a phase II, non-comparative, open-label trial.[3, 33] The trial was designed to assess the safety and efficacy of nivolumab as a monotherapy and in combination with other agents includes several different cohorts (described in Section 3.2.1). The focus of this submission will be on the cohort of patients with recurrent or metastatic CRC that received combination treatment with NIVO+IPI, which hereafter will be referred to as CheckMate 142.

Patients enrolled in CheckMate 142 had histologically confirmed metastatic or recurrent CRC, assessed as dMMR and/or MSI-H, and disease progression following (or intolerance of) ≥1 prior treatment(s) which must include a fluoropyrimidine-based combination chemotherapy (at least a fluoropyrimidine in combination with oxaliplatin or irinotecan). As described in Section 2.2, most patients will be given either FOLFOX or FOLFIRI as first line therapy for mCRC in UK clinical practice. As such, the ERG's clinical experts consider the prior therapies of the population enrolled in CheckMate 142, but also other patient characteristics, to be representative of patients in England likely to be eligible for treatment with NIVO+IPI. A more detailed discussion of baseline characteristics is available in Section 3.2.3.

As the data for NIVO+IPI is from a single arm trial, data for the comparators of interest are based on other trials which are compared with CheckMate 142 in naïve comparisons as well as in matching adjusted indirect comparisons (MAICs) (Section 3.4). Unlike CheckMate 142, in which all patients had MSI-H/dMMR mCRC, the comparator studies all enrolled patients with mCRC but MSI-H/dMMR status was either not reported, or only a very small proportion of patients had MSI-H/dMMR mCRC. As described in Section 2.2, patients with MSI-H/dMMR mCRC constitutes a very small proportion of patients with mCRC and although evidence is mixed, clinical expert opinion is that these patients have a worse prognosis and a worse response to conventional chemotherapy treatments. It is possible that the efficacy of each treatment could differ depending on if a patient has MSI-H/dMMR or not. The difference in populations between the populations in CheckMate 142 and the comparator trials could therefore have an impact on the relative clinical effectiveness of NIVO+IPI, but because of the lack of overlap between the populations this can't be adjusted for using e.g. MAIC.

2.3.2 Intervention

At the time of writing, NIVO+IPI does not have a UK marketing authorisation for mCRC. The expected date of the opinion from the Committee for Human Medicinal Products (CHMP) is ▮▮▮▮▮▮▮ with regulatory approval expected in ▮▮▮▮▮▮▮ .

Nivolumab and ipilimumab are given as intravenous infusions.[34, 35] In CheckMate 142 nivolumab was given at a dose of 3mg/kg together with ipilimumab at 1mg/kg every 3 weeks for 4 doses followed by nivolumab monotherapy 3mg/kg every 2 weeks.[33] The anticipated market authorisation specifies a fixed dose of nivolumab of 240mg every 2 weeks. The ERG's clinical experts commented that the two dosing schedules for nivolumab are expected to be of equivalent clinical effectiveness.

In CheckMate 142 patients continued nivolumab therapy until disease progression or unacceptable toxicity whereas the draft Summary of Product Characteristics (SmPC) recommends that nivolumab therapy is continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.[33, 34] This means that treatment may be continued beyond progression if a patient is deemed to still derive a clinical benefit or discontinued prior to progression in patients with limited clinical benefit.

In the economic model the company has applied a stopping rule at 2 years for nivolumab (base case analysis) and provided a scenario analysis where no stopping rule is applied. In CheckMate 142 no formal stopping rule was used for nivolumab but a protocol amendment in Feb 2019 included an optional stopping point at 2 years for patients assessed as having achieved maximum clinical benefit at this stage. The company highlights that in other indications a stopping rule at 2 years is frequently applied for nivolumab and, according to the company's clinical experts, it is considered clinical practice in the treatment of mCRC (i.e. nivolumab monotherapy is currently available through the Covid interim fund). The ERG's clinical experts fed back that their preference would be to continue nivolumab treatment until disease progression and not to take patients off nivolumab treatment if they are still deriving a benefit and remain progression-free at 2 years. The implications of the 2-year stopping rule for nivolumab for the cost effectiveness of NIVO+IPI are described and critiqued in Section 4.2.6.1.3 and Section 4.2.6.1.4, respectively.

2.3.3   Comparators

The NICE final scope specifies the comparator of interest for this appraisal as single-agent irinotecan, FOLFIRI, FOLFOX, raltitrexed, trifluridine-tipiracil (TRI-TIP), or best supportive care (BSC). Based on advice from clinical experts, the ERG agrees with the company that the comparators most relevant to the decision problem and those explored in this report are:

- FOLFOX;
- FOLFIRI;
- TRI-TIP;
- BSC.

According to the company's and ERG's clinical experts, single-agent irinotecan and raltitrexed are only used for a very small number of patients with mCRC who have had at least one prior therapy. The company has provided clinical and cost effectiveness results for all comparators listed in the scope, but the analyses and results versus single-agent irinotecan and raltitrexed are not discussed further in this report.

The company identified just under 200 studies that could inform the efficacy of the comparators of interest. However, no studies (RCT or other study designs) were identified that provides a direct comparison of NIVO+IPI versus any of the individual comparators (discussed in more detail in Section 3.1), and no network of trials could be connected in order to perform a network meta-analysis (NMA). Due to the lack of common comparator which would enable an NMA or an anchored indirect comparison, the company has provided three different analyses to estimate the efficacy of NIVO+IPI relative to the comparators of interest:

- naïve comparisons of CheckMate 142 versus individual comparator studies;
- unanchored MAICs of CheckMate 142 versus individual comparator studies;
- naïve or unadjusted comparisons of a pooled estimate of NIVO+IPI studies versus pooled estimates of all studies for each comparator.

The ERG broadly agrees with the company's choice of individual studies for the naïve and MAICs with CheckMate 142. Each study was assessed for suitability with particular reference to the treatment pathway most relevant to the UK MSI-H/dMMR mCRC patient population, data availability and reported patient characteristics comparable to CheckMate 142. The choice of and descriptions

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of the individual comparator studies are described in Section 3.4.1, and the merits of the company's different analyses, and the ERG's preferred analysis are described and discussed in Sections 3.4.3 and 3.4.4.

2.3.4 Outcomes

PFS and OS data are immature at the February 2019 data cut presented in the CS. An updated data cut for CheckMate 142 became available at the clarification stage of this appraisal, providing more mature data for PFS and OS. Data for both data cuts are presented in Section 3.3.1 and Appendix 1.1 of this report. Unfortunately, only aggregate data were available for the latest data cut and therefore these data could not be used to inform the MAICs versus the comparators of interest, which relies on the availability of individual patient data (IPD). IPD for the most recent data cut may become available during the technical engagement phase of this appraisal.

3   Clinical effectiveness

3.1   Critique of the methods review

The company undertook a broad systematic literature review (SLR) to capture studies of interventions for the treatment of metastatic colorectal cancer. Full methods and results of the SLR are reported in Appendix D of the company submission (CS). A summary of the methods, together with the Evidence Review Group's (ERG's) critique of the appropriateness of the methods adopted, is presented in Table 13.

The purpose of the SLR was to identify all relevant studies that could inform the comparison of NIVO+IPI with other interventions for previously treated MSI-H or dMMR mCRC. CheckMate 142 is one of the only trials evaluating clinical effectiveness of interventions in previously treated mCRC that is MSI-H or dMMR. As such, the company used broader inclusion criteria, including studies that met all other criteria, but not mentioning MSI or dMMR.

The company included 194 studies reporting over 366 publications in its evidence synthesis, although the ERG notes that, due to the nature of the matched-adjusted indirect comparison, only 1-2 studies were selected for the main analysis of each comparator. During the clarification stage, the ERG requested further information on the company's approach to selecting studies for inclusion in the MAIC (see Section 3.4.1 for full details on the company's selection process).

Overall, the ERG had some concerns that all relevant studies may not have been retrieved. The ERG considers the search strategies to be inconsistent and lacking comprehensiveness. This leads to uncertainty in whether all relevant studies have been captured in the CS and, as a consequence, further uncertainty in the choice of studies informing the MAICs (see Section 3.4.1). Nonetheless, the ERG's clinical experts were not aware of any additional studies in the population of interest (MSI-H/dMMR mCRC). While the ERG considers it likely that studies have been missed, it is less likely that any missed studies were in the population of interest.

Table 13 below provides a summary of the ERG's critique and a more detailed critique is provided in Appendix 9.1.

Table 13. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	Appendix D.1.1.	**The ERG considers the sources and dates searched appropriate.** Databases searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials. Additional sources: Trial registry (clinicaltrials.gov), conference proceedings (ASCO, ESMO and ASCO Gastronintestinal Cancers Symposium), HTA agency websites (NICE, SMC, AWMSG, CADTH, PBAC) Latest search update: 26 June 2020
Search terms	Appendix D.1.1. Tables 1–6	**The ERG is concerned that studies relevant to the decision problem may have been missed.** The ERG considers that search terms for the population, interventions and outcomes were too specific (see Section 9.1 for further details), and that search terms for interventions were not used sufficiently nor consistently across each search strategy. The ERG considers the study design search terms to be appropriate.
Inclusion criteria	Appendix D.1.1. Tables 7 and 8	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** Inclusion criteria for the population of interest were broader than the NICE final scope, including studies in mCRC and not just those in MSI-H/dMMR mCRC. Lists of studies excluded at full-text appraisal together with reasons for exclusion are provided, although the ERG notes that reasons for exclusion were lacking in detail. Limited to English-language publications.
Screening and data extraction	Appendix D.1.1	**The ERG considers the methods for screening and data extraction to be sufficient.** Independent duplicate screening and data extraction were conducted by two reviewers against predefined criteria, with discussions used to reach consensus if disagreement arose between the two assessments. It is however unclear what approach was taken if agreement was not reached by the two reviewers. Screening results summarised in a PRISMA diagram.
Tool for quality assessment of	Appendix D.1.3. Tables 23–26	**The ERG agrees with the use of ROBINS-I as the quality assessment tool used for CheckMate 142 (although notes**

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included study or studies		**that there is no established quality assessment tool for single arm studies).**
		Quality ratings for the other studies informing the MAIC are unclear (see Section 9.1.2 for further detail)
		The ERG notes that it is unclear if quality assessment was done by one or two reviewers and, if so, whether the assessments were done independently.

Abbreviations: ASCO, American Society of Clinical Oncology; AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; CS, company submission; dMMR, mismatch repair deficient; ERG, Evidence Review Group; ESMO, European Society for Medical Oncology; HTA, health technology appraisal; MAIC, matched adjusted indirect comparison; mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PBAC, Pharmaceutical Benefits Advisory Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; ROBINS-I, Risk Of Bias In Non-randomised Studies - of Interventions; SMC, Scottish Medicines Consortium.

3.2 Critique of trials of the technology of interest

The company identified two studies assessing the efficacy and safety of NIVO+IPI in their SLR; NIPICOL[36] and CheckMate 142.[3, 33] The company has also presented supporting evidence for NIVO+IPI from Lam *et al.* 2020,[37] a small UK real-world evidence study of nivolumab monotherapy and NIVO+IPI (CS, Section B.2.13.4.1).

In the following sections, the Evidence Review Group (ERG) focuses on aspects of trial design, conduct and external validity of the key study, CheckMate 142, that are of importance to this Single Technology Appraisal (STA). The design and conduct of CheckMate 142 are summarised in Table 14 and a summary of the alternative data sources for NIVO+IPI is provided in Section 3.2.4.

Table 14. Summary of CheckMate 142 methodology

Aspect of trial design or conduct	Section of CS in which information is reported	Description
Study design	B.2.2.1., B.2.3.1 and B.2.4.2.	Phase II, open-label, non-randomised trial with a two-stage Simon design described in **Section 3.2.1**
Eligibility criteria	B.2.3.2.	Adults with histologically confirmed metastatic or recurrent CRC, assessed as dMMR and/or MSI-H, and disease progression following (or intolerance of) ≥1L treatment(s), which must include at least (i) a fluoropyrimidine, and (ii) oxaliplatin or irinotecan. Patients who refused chemotherapy for the treatment of metastatic or locally advanced disease were also eligible. Eligibility included ECOG performance status of 0 or 1 and measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1).

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| Biomarker analyses | B.2.3.1. | MMR/MSI status was detected by an accredited laboratory as per local regulations (IHC or PCR).

For PCR, individual testing sites were allowed to utilise a slightly different panel of markers incorporating alternative mononucleotide and/or dinucleotide markers. Regardless of the panel of markers, samples with instability in 30% or more of these markers were defined as MSI-H, whereas those with < 30% unstable markers were designated as MSI-low (MSI-L); samples with no detectable alterations were MSS.

For IHC, there were four antibody markers to determine protein expression from the four MMR genes in the panel. Samples with loss of protein expression in one or more genes were defined as dMMR; those with intact protein expression in all four genes were defined as pMMR. Samples were subsequently centrally tested by PCR. |
|---|---|---|
| Baseline characteristics | B.2.6.1.1 | Patients in CheckMate 142 are broadly representative of patients likely to be treated with NIVO+IPI in UK clinical practice. Baseline characteristics are available in Appendix 9.1, Table 52 of the ERG report and discussed in **Section 3.2.3**. |
| Study medication | B.2.3.3. | All patients who met eligibility criteria and were enrolled into the NIVO+IPI arm received NIVO 3mg/kg (60-minute intravenous [IV] infusion) and IPI 1 mg/kg (90-minute IV infusion) once every 3 weeks for four doses and then nivolumab 240mg IV once every 2 weeks until disease progression, discontinuation due to toxicity, death, withdrawal of consent, or study end. Dose modifications were not permitted. Dose interruptions for treatment related adverse events (TRAEs) were allowed. |
| Dropouts and missing data | B.2.4.1. and B.2.6.1.3. | It is unclear from the CS if there were any dropouts, i.e. withdrawal of consent during the study.

Patients who did not have any on study tumour imaging assessments and did not die were censored on the first dosing date.

For patient reported outcomes (PRO) patients with missing baseline or post-baseline assessments were excluded from the analysis. |
| Outcome assessment | B.2.3.4. and B.2.6.1.3.1. | The primary endpoint is investigator-assessed ORR.

ORR and PFS were reported both based on investigator assessment and based on BICR assessment. Tumour imaging assessments occurred every 6 weeks for the first 24 weeks, then every 12 weeks.

Patient-reported outcomes were captured using EORTC QLQ-C30 & EQ-5D questionnaires. EORTC QLQ-C30 was assessed prior to first dose on day 1 and every 6 weeks thereafter, with additional follow-up at follow-up visit 1 and 2.

███ |
| Analysis population | B.2.4.1. | Efficacy analyses were performed for the treated population, defined as all patients who received at least one dose of study medication within a given cohort of CheckMate 142. The relevant cohort for this appraisal is of patients with recurrent or metastatic CRC that received combination treatment with NIVO+IPI. |

Subgroup analyses	B.2.7.	IA and BICR-assessed ORR using RECIST 1.1 was compared across several baseline subgroups discussed in Section 3.3.1 and the results of which are presented in Appendix 1.1, Table 53 and Table 54.
Statistical analysis plan		
Null hypothesis	B.2.4.2.	A Simon optimal two-stage design was used to test the null hypothesis that the true ORR is ≤ 30% (not considered clinically compelling) with treatment.
Sample size and power	B.2.4.2.	The null hypothesis was to be rejected if 20 or more responses were observed in 48 treated patients (ORR 42%). This design yields a one-sided type I error rate of 5% and power of 90% when the true response rate is 52%.
Analysis for estimate of effect	B.2.4.1.	ORR was summarised using a response rate estimate and corresponding two-sided 95% exact CI. The CI was estimated using the method proposed by Atkinson and Brown as this CI takes into account the group sequential nature of the two-stage Simon design. PFS and OS was summarised using the KM product-limit method. Median values of PFS and OS, along with two-sided 95% CI (based on the log-log transformation), was calculated.
Censoring	B.2.4.1.	When assessing OS, a patient who had not died was censored at their last known date alive. Similarly, when assessing PFS, patients who did not progress or died were censored on the date of their last evaluable assessment. Patients who did not have any on study tumour imaging assessments and did not die were censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable assessment prior to initiation of the subsequent anti-cancer therapy.
Quality assessment		
Risk of bias assessment	B.2.5.	The company's quality assessment of CheckMate 142 using ROBINS-I can be found in the CS Table 8 and discussed in **Section 3.2.2.**

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CRC, colorectal cancer; CS, company submission; dMMR, mismatch repair deficient; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, the European Organization for Research and Treatment of Cancer quality of life questionnaire; ERG, Evidence Review Group; EQ5D, EuroQol-5D; IHC, immunohistochemistry; KM, Kaplan-Meier; mCRC, metastatic colorectal cancer; MMR, mismatch repair; MSI-H, high microsatellite instability; MSI-L, low microsatellite instability; NICE, National Institute for Health and Care Excellence; ORR, overall response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; PRO, patient reported outcomes; RECIST, response evaluation criteria in solid tumours; ROBINS-I, Risk Of Bias In Non-randomised Studies - of Interventions

3.2.1 Study design

CheckMate 142 is a phase II open-label, non-randomised trial with a 2-stage Simon design assessing the response rate of nivolumab monotherapy, NIVO+IPI, or an investigator's choice chemotherapy in patients with MSI-H CRC and non-MSI-H CRC.

Due to the low prevalence of patients with previously treated MSI-H or dMMR mCRC, clinical trial recruitment is severely limited and a single-arm study was deemed ethical and relevant to facilitate a rapid assessment and confirmation of clinical activity of NIVO+IPI in the dMMR/MSI-H mCRC population. However, the company has developed CheckMate 8HW, an ongoing phase IIIb, randomised, open-label multi-centre clinical trial of nivolumab monotherapy, NIVO+IPI, or an investigator's choice chemotherapy in patients with MSI-H/dMMR mCRC to confirm the benefit observed in CheckMate 142. CheckMate 8HW is ongoing with an estimated primary completion date in 2025.[38] However, preliminary results are expected in ███████.

CheckMate 142 included the following cohorts:

- nivolumab alone (mStage);
- NIVO+IPI in previously treated MSI-H patients (cStage) – Note: this forms the basis for the current STA submission;
- NIVO+IPI in previously untreated MSI-H patients (Cohort C3);
- NIVO+IPI and cobimetinib for previously treated non-MSI-H patients (Cohort C4);
- nivolumab in combination with an anti-LAG3 agent for previously treated MSI-H patients (BMS-986016; Cohort C5);
- or nivolumab in combination with daratumumab for previously treated non-MSI-H patients (Cohort C6).

Methods and results are only presented for the cStage cohort, relevant to the proposed indication (NIVO+IPI for the treatment of patients with dMMR or MSI-H mCRC following prior therapy).

In short, the two-stage Simon design is developed to minimise the sample size required by possible early termination after the first stage if the intervention has low activity. The decision of whether or not to terminate after the first stage is based on the number of responses observed in the first stage. In CheckMate 142, 19 patients with previously treated MSI-H were enrolled in stage 1 of the trial arm given NIVO+IPI (cStage 1). If there were 6 or fewer responses in these first 19 treated patients, accrual to the combination arm would have been stopped. Otherwise, approximately 29 additional patients were to be accrued to the combination arm (cStage 2) to target a total of 48 patients treated with combination therapy. The ERG notes that 119 patients were eventually enrolled in the cStage cohort of CheckMate 142.
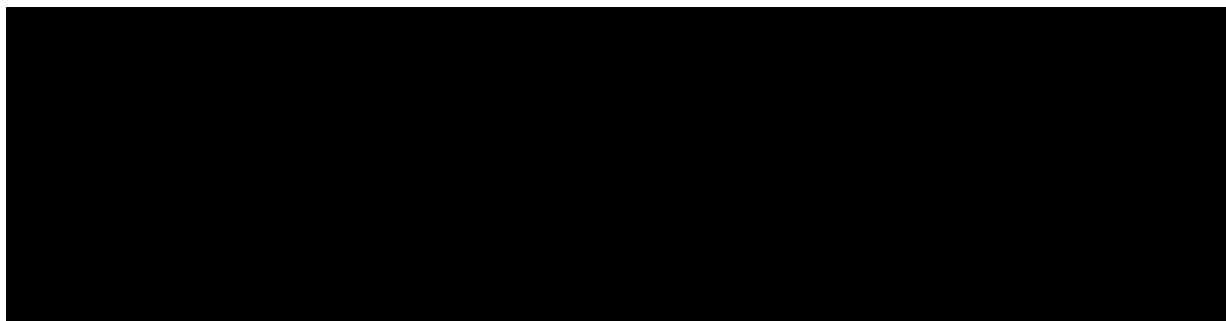
FPFV: first patient's first visit; LPFV: last patient's first visit; q2w: every 2 weeks; q3w: every 3 weeks.

3.2.2 Quality assessment

The company assessed the quality of CheckMate 142 using ROBINS-I, a tool developed for evaluating risk of bias of comparative, non-randomised interventional studies.[39] The company assessed CheckMate 142 as being of low risk of bias for all domains except confounding, which was judged to be of moderate risk of bias. The ERG is not aware of any recognised and validated quality assessment tool for single arm studies but notes that the company, as a minimum, could have adapted the ROBINS-I tool by removing all domains concerning the comparability between intervention and control groups.

In order to better inform interpretation of the results of the indirect comparisons of CheckMate 142 and each comparator study, which consist of data from single arms of two separate studies, the ERG considers that risk of bias assessment should take into account both studies included in each comparison. The company provides a narrative discussion about differences between CheckMate 142 and each comparator study before and after matching, in the CS Appendix L, Section 3. This is further discussed in Section 3.4.1 of this report. In addition, the methods for estimating the residual bias of indirect comparisons like these, are described in Section 3.4.3.3.

In terms of the quality assessment of CheckMate 142 on its own, the ERG considers it to be of reasonable quality for the trial design chosen; risk of bias due to missing data, risk of reporting bias and risk of bias in classification of intervention is likely low. However, risk of bias due to deviations from the intended intervention is unclear; the company has not provided a patient flow diagram or other information around the number of patients who received the wrong dose, withdrew consent, were lost to follow up or stopped treatment for other reasons. The risk of bias in measurement of

outcomes is likely to be high for ORR, PFS and QoL but low for OS. Data for both IA and BICR of both ORR and PFS have been presented but the trial is still single arm and open label, and so patients, clinicians and independent assessors were all aware of the treatment received.

Although all domains in the ROBINS-I tool should be assessed across intervention and comparator arms, there are two domains that the ERG only considers possible to assess in relation to a control group: risk of participant selection bias and risk of bias due to confounding. The risk of confounding was assessed as moderate and the risk of participant selection was assessed as low, by the company. When assessed in relation to each of the comparator studies, the ERG considers it likely that risk of bias for both domains will be serious or critical.

3.2.3   Baseline characteristics

CheckMate 142 is a multi-centre trial with locations in North America (USA and Canada), Australia and Europe (Ireland, Belgium, Italy, France and Spain) but with no UK sites. Clinical experts informing the ERG advised that patients in CheckMate 142 are broadly representative of patients likely to be treated with NIVO+IPI in UK clinical practice. The baseline characteristics are presented in Appendix 9.1, Table 52. Age and ECOG performance status of patients in CheckMate 142 are in line with other clinical trials but slightly younger and better performance status than would be expected for patients in clinical practice.

Patients in CheckMate 142 are also quite heavily pre-treated; 40.4% of patients had received three or more prior systemic regimens. NIVO+IPI is expected to be used primarily second line and so the trial population is more heavily pre-treated than would be expected for patients receiving NIVO+IPI in clinical practice. Subgroup data from CheckMate 142 (Appendix 1.1) indicates a decreasing ORR with an increasing number of prior treatments. That is, the ORR trial results are potentially conservative compared with what could be expected if all patients had been treated with NIVO+IPI second line.

A large proportion of patients in CheckMate 142 had received prior bevacizumab and other treatments, which are not available as treatment options in the UK. However, the ERG's clinical experts advised that these prior treatments are unlikely to affect the efficacy of treatments used second- or third-line.

In order to allow a comparison between the NIVO+IPI and the comparators of interest, the comparability of characteristics of patients in CheckMate 142 and in the comparator studies (both before and after matching) become very important. These are discussed in Section 3.4.1.

3.2.4   Additional NIVO+IPI studies

In addition to CheckMate 142, the company present supporting evidence of the efficacy and safety of NIVO+IPI from two other studies, NIPICOL and Lam *et al.* 2020.[36, 37]

Lam *et al.* 2020 is a small UK real-world evidence study of nivolumab monotherapy (37 patients) and NIVO+IPI (12 patients) in patients with MSI-H/dMMR mCRC (CS, Section B.2.13.4.1). It is a retrospective study conducted by the University College London Hospital as part of the UK BMS Individual Patient Supply Request programme. Median follow-up from start of treatment was relatively short at 17.7 months, median OS was not reached in either treatment group, and median PFS was around 10 months for nivolumab monotherapy but not reached for the NIVO+IPI group. Due to the short follow up and small sample size, it is difficult to draw any conclusions around the differences between the populations and results of Lam *et al.* 2020 and CheckMate 142.

NIPICOL is a French multicentre, phase II, single-arm, open-label study evaluating disease control rate (DCR) of NIVO+IPI treatment in 57 patients with previously treated dMMR/MSI mCRC. At the time of the company submission, NIPICOL was only presented as a conference abstract with limited information available about the study. However, by the clarification stage, a manuscript had been accepted for publication and the company was able to provide more information on this study.

The inclusion criteria and treatment regimen of NIPICOL are similar to CheckMate 142 but in NIPICOL treatment with nivolumab was limited to 20 infusions, equivalent to 1 year of therapy. Median follow-up was short also for this study at 18.4 months. At this point median PFS and OS had not been reached but PFS and OS survival rates at 12 months were 72.9% (95% CI: 59.0% to 82.7%) and 84.0% (95% CI: 71.4% to 91.3%), respectively, which are broadly comparable to CheckMate 142 (see Section 3.3.1).

3.3 Clinical effectiveness results

3.3.1 Primary and secondary outcomes

The results for CheckMate 142 presented in the company submission (CS) are based on a database lock in February 2019.[3] Some additional data from an updated data cut of October 2020 have become available during the appraisal and are also presented here.

At the February 2019 data cut, minimum follow-up was ▮▮▮ months and median follow-up ▮▮▮ months. The primary endpoint of CheckMate 142 is investigator assessed (IA) objective response rate (ORR). At the February 2019 data cut IA ORR was ▮▮▮▮▮▮▮▮▮▮▮▮▮▮ and ORR as assessed by blinded independent central review (BICR) was ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮. Median progression-free survival (PFS) was ▮▮▮ months per IA and ▮▮▮ months per BICR (Figure 6 and Figure 7, respectively). Median overall survival (OS) (Figure 8) and median duration of response (DOR) ▮▮▮▮▮▮▮▮▮▮▮ at the February 2019 data cut. The 12-month, and 24-month OS rates were 84.9% and ▮▮▮▮, respectively.

The updated data cut (October 2020), which provides observed data up to five years, supports the continued benefit of NIVO+IPI. Median OS and IA PFS was ▮▮▮▮▮▮ and median PFS per BICR was ▮▮▮▮▮▮ (see Appendix 1.1 for KM figures and further details).

In terms of response, the IA results are generally consistent with the BICR results, although, there were differences in

▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ and ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮.

The company concludes that NIVO+IPI therapy demonstrated a clinically meaningful effect on efficacy endpoints including ORRs, DCR, DOR, PFS per IA and per BICR, and OS. The ERG's clinical experts commented that similar results have never been seen before for this patient population, which they consider having a very poor prognosis. However, the ERG notes that results tend to be better in open label, single arm trials than in double blind RCTs. This means that the results of CheckMate 142, as a relatively small single arm study, may show quite different absolute results than would be expected if it had been a double blind RCT or what would be expected in UK clinical practice. In addition, CheckMate 142 does not provide any comparative data to show how much better NIVO+IPI is than any of the relative comparators. The robustness of the naïve and matching

adjusted indirect comparisons (MAIC) performed by the company are described and critiques in Section 3.4.

Table 15. CheckMate 142 results (February 2019 DBL, adapted from CS Table 10 and clarification response A3)

Endpoint	NIVO+IPI (n=119) BICR assessed	NIVO+IPI (n=119) Investigator assessed
ORR, n (%) [95% CI]	███████████	███████████
DCR, n (%) [95% CI]	███████████	███████████
Best Overall Response		
Complete response, n (%) [95% CI]	██████████	█████████
Partial response, n (%) [95% CI]	██████████	███████████
Stable disease, n (%)	█████	█████
Progressive disease, n (%)	█████	█████
Unable to determine, n (%)	████	████
Duration of response (DOR)		
Median (95% CI)	████████	████████
Patients with ongoing response, n (%)	█████	█████
Progression-free survival (PFS)		
Number of events (%)	█████	█████
Median, months (95% CI)	█████████	█████████
3 months, % (95% CI)	█████████	NA
6 months, % (95% CI)	█████████	█████████
9 months, % (95% CI)	█████████	NA
12 months, % (95% CI)	█████████	71.6 (62.5 to 78.9)
24 months, % (95% CI)	█████████	█████████
30 months, % (95% CI)	█████████	NA
Overall survival (OS)		

Number of events (%)		██████
Median, months (95% CI)	-	███████
3 months, % (95% CI)	-	█████████
6 months, % (95% CI)	-	█████████
9 months, % (95% CI)	-	87.4 (80.0 to 92.2)
12 months, % (95% CI)	-	84.9 (77.1 to 90.2)
24 months, % (95% CI)	-	█████████
30 months, % (95% CI)	-	█████████

Figure 2. Investigator-assessed progression-free survival: February 2019 database lock[40] (reproduced from CS, Figure 6)

Figure 3. Overall survival from CheckMate 142: February 2019 database lock (reproduced from CS, Figure 8)

The company reported results for pre-specified subgroup analyses for investigator-assessed and BICR-assessed ORR across baseline subgroups. Results of these subgroup analyses are reported in Appendix 1.1, Table 53 and Table 54. For both IA and BICR assessed ORR there were several subgroups for which at least 10% difference was noted in the response rate between the subgroups. The company did not report any assessment of statistically significance between subgroups but the ERG notes that none of the subgroup analyses are likely to be powered to detect a significant difference due to the small sample sizes.

3.3.2 Quality of life

Quality of life was assessed in CheckMate 142 using EORTC QLQ-C30 and EQ-5D-3L. EQ-5D is reported as an index score and a visual analogue scale (VAS). EORTC QLQ-C30 are reported on a scale of 0–100 with higher values indicating better quality of life with changes from baseline of at least 10 points considered clinically meaningful.

Of the 119 patients treated with NIVO+IPI in the trial, 107 patients were included in the analysis of quality of life. Two patients were excluded due to no PRO data available, two were excluded due to missing baseline assessment, and eight were excluded due to missing post-baseline assessments.

The company reports

███)

in global quality of life with NIVO+IPI treatment, as assessed by EORTC QLQ-C30,

██

████████████████ (Figure 4).

The company also reports that

██

██

██

██

██. ██████████████.[41]

Figure 4. EORTC QLQ-C30: Mean change from baseline in global health status[41] (reproduced from CS, Figure 9)
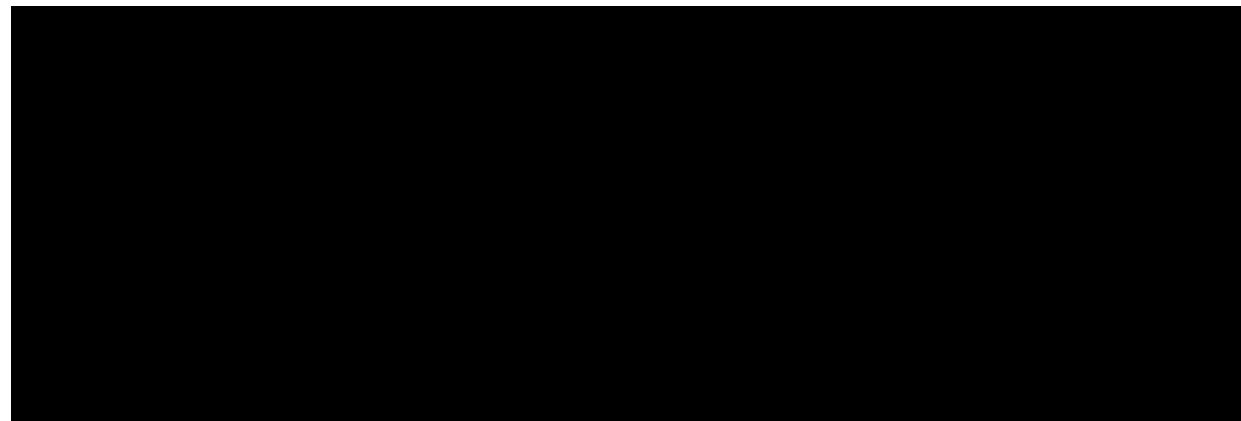
Patients treated with NIVO+IPI demonstrate ████████████████████████████ Figure 5██████████████████ (Figure 6██ ██████████████████████████████ Figure 5. EQ-5D-3L: Index score mean change from baseline[41] (reproduced from CS, Figure 10)
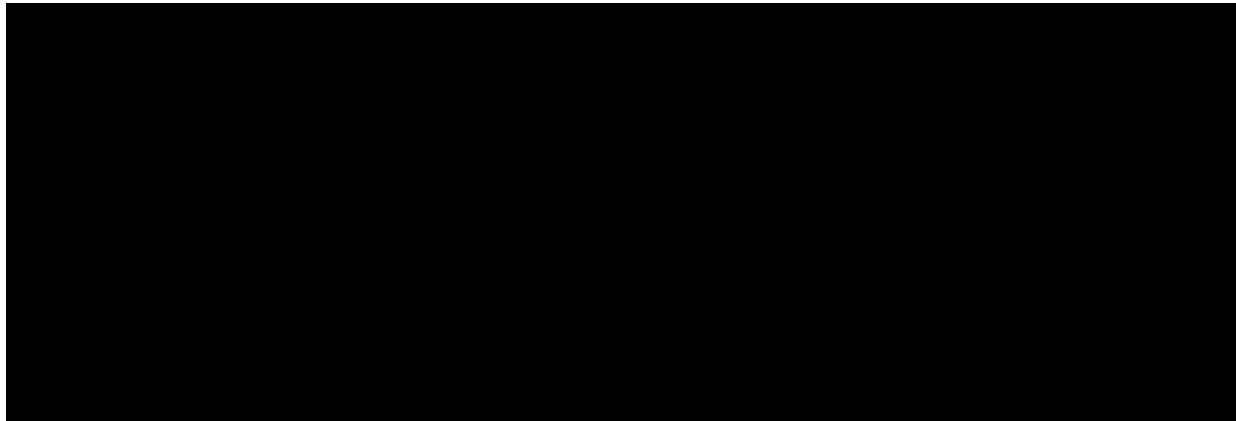
Figure 6. EQ-5D-3L: VAS mean change from baseline[41] (reproduced from CS, Figure 11)
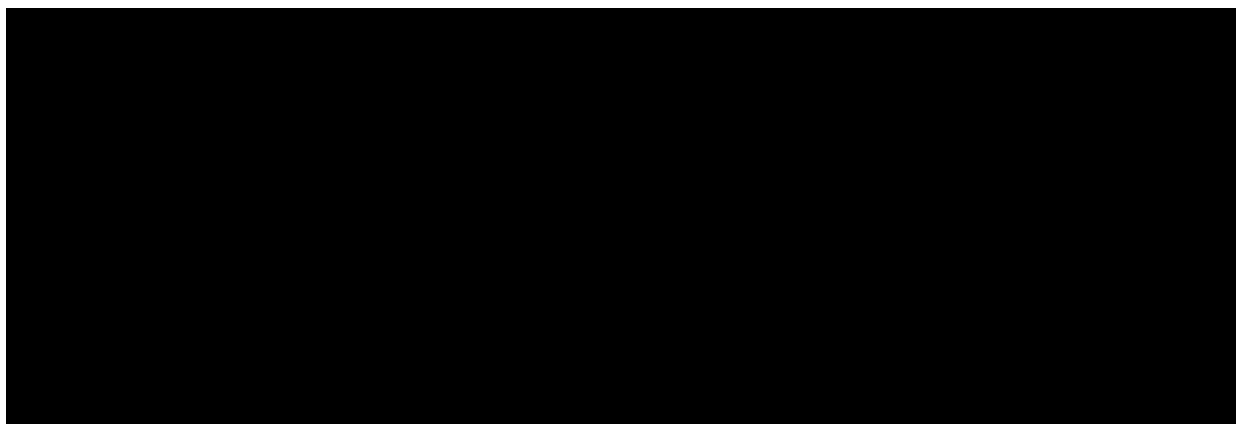
3.3.3 Safety

Exposure

At the February 2019 data cut, ███████████ of patients received 90% to 110% of the planned dose intensity of nivolumab and ipilimumab, respectively (Table 56). ████ patients received ███████ doses of ipilimumab (████████████) and the median number of doses of nivolumab was ██ (Appendix 9.6, Table 56), equivalent to a median duration of treatment of ████ months. At the data cut, ██ patients continued to receive nivolumab therapy post progression.

Dose modifications were not permitted during CheckMate 142 but dose interruptions or dose delays were allowed for treatment related adverse events (TRAEs). However, it is unclear how many patients had dose interruptions and for how long, due to TRAEs.

Adverse events

██ patients (█████) in CheckMate 142 experienced at least one adverse event (AE) (Appendix 9.6, Table 57). The company reported that the most common AEs of any cause were ███. Grade 3-4 AEs occurred in █████ of patients. The most common Grade 3-4 AEs were ██ ███████████████████████████████████ Serious adverse events (SAEs) were reported in ████ of patients, and Grade 3–4 SAEs were reported at a frequency of █████. AEs leading to treatment discontinuation were reported in █████ of patients (any-grade), and █████ of patients (Grade 3–4).

Treatment-related adverse events (TRAEs) of any grade were reported in █████ of patients (Appendix 9.6, Table 57). The ERG notes that the rates of TRAEs in Table 18 of the CS differ slightly to the text in Section B.2.10.1.4. According to Table 18, the most common TRAEs were █████████████ █████████████████████████. A total of ██. Treatment-related SAEs were reported in █████ of patients, and Grade 3-4 treatment-related SAEs were reported at a frequency of █████. TRAEs leading to discontinuation were reported at a frequency of █████████ any grade) and █████ (Grade 3–4).[40]

At the February 2019 data cut, █████████) patients had died. No deaths were attributed to study drug toxicity and the majority of deaths were due to underlying disease progression (██).

Adverse events of special interest

The ██. The most common AESIs by category were skin (███████), gastrointestinal (███████), and hepatic (███████) (Appendix 9.6, Table 58). The company reports that the majority of AESIs were manageable using the recommended treatment guidelines for early work up and intervention. ████████████████████████████████████ by the investigator. The most frequently reported treatment-related AESI categories (any grade) were ████████████████████████████ (Appendix 9.6, Table 58).

Across the AESI categories, the majority of events were manageable using the established algorithms, with resolution occurring when immune-modulating medications (mainly systemic

corticosteroids) were administered. ████ of patients received corticosteroid for adverse event management.

██

██

██. ████ of patients received hormone replacement therapy for adverse event management.

3.4   Indirect treatment comparison

No studies have been identified that provide a direct comparison of NIVO+IPI versus any of the comparators of interest, and no network of trials could be connected in order to perform a network meta-analysis (NMA). As outlined in Section 2.3, due to the lack of a common comparator which would enable an NMA or an anchored MAICs, the company has performed adjusted (unanchored MAICs) and unadjusted (naïve) comparisons to assess the relative efficacy of NIVO+IPI versus the comparators listed in the NICE final scope.[28]

The naïve comparisons presented by the company are of both individual studies and between pooled estimates of all studies informing NIVO+IPI and each comparator. The ERG does not consider the pooled analysis to be appropriate as an unadjusted pooled comparator estimate is likely to be for a population which is less like CheckMate 142 than the most similar individual study. In addition, an assessment of how similar or different all the individual study populations are from CheckMate 142 were not provided, neither were sensitivity analyses exploring the impact of limiting the analysis to studies with a population more similar to CheckMate 142. The ERG, therefore, considers an analysis comparing CheckMate 142 with the most relevant individual comparator study to be more robust. For details of the pooled analysis and the ERG's critique of it, see Appendix 9.8.

The following sections provide a summary and critique of the naïve and adjusted comparisons of individual studies.

The company assessed each comparator study for suitability for indirect comparison with NIVO+IPI, with particular reference to treatment pathway most relevant to the UK MSI-H/dMMR mCRC patient population, data availability and reported patient characteristics comparable to CheckMate 142. The ERG notes that all comparator studies were in the mCRC population where MSI-H/dMMR status either wasn't reported, or only a very small proportion of patients had MSI-H/dMMR mCRC.

However, the ERG broadly agrees with the company's choice of individual studies. The company's selection of individual comparator studies is provided in Section 3.4.1.

The company used mean survival as the effect measure for the MAICs and naïve comparisons. In Section 3.4.2., the company's estimation of mean survival for NIVO+IPI and the comparators are briefly described, but the underlying survival modelling of NIVO+IPI is described in detail in Section 4.2.6.1. For NIVO+IPI, the company estimated mean survival using semi-parametric survival models with KM data up to 6.44 months followed by an extrapolation of the KM data using standard parametric survival curves and calculation of the area under the curve. The ERG considers piecewise modelling with KM data up to 2.99 months the most plausible for both PFS and OS. The alternative modelling of NIVO+IPI and its impact on both the naïve and adjusted comparisons is presented in Section 3.4.2 and Section 3.4.4, and the corresponding cost effectiveness is presented in Section 6.

A naïve or unadjusted indirect comparison will be biased due to imbalances in observed and unobserved prognostic factors and treatment effect modifiers between the study populations. The bias may be reduced by appropriate use of MAIC. For an unanchored MAIC it is effectively assumed that outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet as clearly it is not possible to adjust for unobserved treatment effect modifiers and prognostic variables in such an analysis. However, in order to minimise bias and more reliably predict outcomes, the NICE DSU TSD 18 recommends that all observed effect modifiers and prognostic variables be adjusted for in unanchored MAICs.[42]

Usually reporting in published papers prohibits a full adjustment of all prognostic factors and treatment effect modifiers even if all of these factors are known, which means that some differences will remain and with them an unknown amount of residual bias. In addition, there are usually some differences that can't be adjusted for, such as heterogeneity due to differences in study design and study conduct. A potentially important difference between the studies in this appraisal, which can't be adjusted for, is that no comparator studies were identified in the population of interest, i.e. MSI-H/dMMR mCRC. According to the company and the ERG's clinical experts, patients with MSI-H/dMMR mCRC may have a considerably worse prognosis than the overall mCRC population. However, the prevalence of MSI-H/dMMR mCRC is low and there is currently a paucity of evidence, especially in the recurrent setting, to support a worse prognosis in this population.

The company performed MAICs using different sets of covariates; either partially adjusted (select covariates) or fully adjusted (all reported covariates). The company base case is based on partially adjusted MAICs as it considers the partial adjustment to minimise uncertainty without increasing the bias. The company states that unanchored MAICs have to make trade-offs between effective sample size (ESS) and the number of adjustment variables. The ERG considers the resulting trade-offs between ESS and the number of adjustment variables to only be valid in an anchored MAIC. In an unanchored MAIC, the ERG preference would be to have a more accurate, if less precise, estimate based on adjustment of all available variables, as recommended in DSU TSD 18.[43]

A priori, it is not possible to predict the impact of all possible adjustments that need to be made within an unanchored MAIC. Individual adjustments may increase or decrease the difference in benefit between the treatments evaluated. As such, partial adjustments (as the company prefers) may potentially increase the bias compared to a naïve comparison or give a false impression of increased accuracy (compared to a naïve comparison) or precision (compared to a fully adjusted comparison). However, the results of the MAICs adjusted for all available covariates, although less biased than the partially adjusted analyses, result in very small effective sample sizes (ESS) which makes the results potentially unreliable. However, the low ESS also gives an indication of how different the populations of CheckMate 142 and the comparator studies are from each other.

In the absence of a valid fully adjusted MAIC, the ERG's preferred approach is the use of a naïve comparison as it is transparent in terms of the likely biases that exist within the comparison and the analysis itself has not introduced additional bias into the comparison. However, the ERG highlights that there is an unquantifiable but likely very large amount of uncertainty around all the results presented, both adjusted and unadjusted.

A more detailed description and critique of the methods and results of the company's MAICs are provided in Sections 0 and 3.4.4, respectively.

3.4.1 Trials identified and included in the indirect comparisons

The company identified 194 studies relevant to the decision problem of this appraisal. From these, the company selected individual comparator studies which were used for naïve comparisons and MAICs versus CheckMate 142. The company has chosen one study to inform the comparison with each comparator for the base case, with alternative studies chosen for scenario analyses based on similar relevance. Each study was assessed for suitability for comparison with CheckMate 142 with

particular reference to the UK MSI-H/dMMR mCRC patient population, data availability and comparability to the CheckMate 142 baseline characteristics.

Although the company described the criteria applied for choosing individual studies (Appendix 9.7) it is not clear from the CS how the company chose these studies over other potentially suitable ones. At the clarification stage the ERG asked the company to provide the rationale for selecting a specific study for each comparison, and the rationale for excluding each of the other included studies (clarification response A10). The ERG also requested that the comparator studies be re-assessed using a slightly different set of criteria (Appendix 9.7). The company's choice of studies to inform their base case did not change after re-assessment, but the company did supply scenario analyses versus alternative data sources, including for the comparator study with the best outcomes, as a conservative approach. The ERG broadly agrees with the company's choice of individual studies but has a different opinion on which trials to use for the base case and for scenario analyses. The company's and ERG's study selection for each of the indirect comparisons with NIVO+IPI are listed in Table 16, and discussed in the following sections of the report.

As mentioned in Section 2.3.3, single-agent irinotecan and raltitrexed are only used for a very small number of patients with mCRC who have had at least one prior therapy and was therefore not considered relevant comparators. Although the company provided clinical and cost effectiveness results for all comparators listed in the scope, including single-agent irinotecan and raltitrexed (CS, Section B.2.9.), these are not discussed in this report.

Table 16. Studies selected by the company and by the ERG for base case and scenario analysis

Intervention	Study chosen for MAIC informing the company base case		Study used in scenario analysis		Study with most optimistic outcome data used in scenario analysis
	Company	ERG	Company	ERG	Company
FOLFIRI	VELOUR[44]	VELOUR[44] and RAISE[45]	RAISE[45]		NCT01479465[46]
FOLFOX	CONFIRM2[47]	CONFIRM2[47]	NO16967[48]	NO16967[48]	CAPRI-GOIM[49]

TRI-TIP	RECOURSE/EUR[50]	RECOURSE/EUR[50]	RECOURSE/USA[50]		TERRA[51]
BSC	RECOURSE/EUR[50]	RECOURSE/EUR[50]	LUME-colon 1[52] and RECOURSE/USA[50]	LUME-colon 1[52]	TERRA[51]

Abbreviations: BSC, best supportive care; ERG, evidence review group; FOLFIRI, folinic acid, 5-fluorouracil, irinotecan; FOLFOX, folinic acid, 5-fluorouracil, oxaliplatin; MAIC, matching adjusted indirect comparison; TRI-TIP, trifluridine-tipiracil

Unlike CheckMate 142, the selected comparator studies were all RCTs and all in the mCRC population where MSI-H/dMMR status either wasn't reported, or only a very small proportion of patients had MSI-H/dMMR mCRC. Where reported, a majority of patients in the comparator studies as well as in CheckMate 142 had received prior bevacizumab, which is not recommended in UK practice. The ERG's clinical experts comment that prior bevacizumab therapy is unlikely to affect the efficacy of NIVO+IPI or the efficacy of the comparators. Several of the comparator studies also included patients with a performance status of 0-2, whereas CheckMate 142 is limited to ECOG 0-1. However, the proportion of patients with an ECOG performance status of 2 was low in all trials which included them and is therefore unlikely to have a large impact on the comparability of CheckMate 142 and each of the comparator studies.

3.4.1.1 FOLFIRI

VELOUR[44] is a large (the FOLFIRI arm includes 614 patients), phase III, multinational, double-blind RCT. It aimed to evaluate the efficacy and safety of aflibercept plus FOLFIRI versus placebo plus FOLFIRI in patients with mCRC following disease progression while on or after completion of treatment with an oxaliplatin-based regimen. Patients were permitted to have received oxaliplatin as adjuvant therapy provided that relapse was within 6 months of completion of this therapy. In the placebo/FOLFIRI arm, 10.4% had received adjuvant therapy only, a proportion of patients for which there is no overlap with the CheckMate 142 population. Patients enrolled in VELOUR could also have an ECOG performance status of 0-2 though the proportion with ECOG of 2 was low (2.3%).

RAISE[45] is another large (the FOLFIRI arm includes 536 patients), phase III, multinational, double-blind RCT. This trial aimed to investigate whether ramucirumab plus second-line chemotherapy would be associated with prolonged survival in patients with mCRC whose disease had progressed during or after first-line treatment including bevacizumab. That is, all patients in RAISE had received

bevacizumab therapy prior to entering the trial compared with 57.1% who had received prior therapy with a VEGF inhibitor in CheckMate 142.

NCT01479465[46] represents the FOLFIRI study with the best PFS and OS outcome data. It is a phase II, double-blind, multicentre USA-based, RCT with only 80 patients in the FOLFIRI arm. The trial evaluated the efficacy of simtuzumab or placebo in combination with FOLFIRI in patients with KRAS-mutant mCRC who progressed following oxaliplatin- and fluoropyrimidine-containing first-line therapy. In comparison, 37% of patients in CheckMate 142 had a KRAS mutation.

The ERG agrees with the company that VELOUR and RAISE are the most relevant studies to inform the comparison with FOLFIRI, but that both studies have specific limitations in terms of the trial population compared with CheckMate 142.

3.4.1.2 FOLFOX

CONFIRM 2[47] is a phase III, multinational, double blind RCT, which enrolled patients with mCRC whose disease had recurred or progressed during or within 6 months of first line treatment with irinotecan in combination with a fluoropyrimidine. Patients were randomised to FOLFOX-4 plus vatalanib or FOLFOX4 plus placebo. It is a large trial with 429 patients in the FOLFOX-4 plus placebo arm, measurable disease at baseline was an enrolment criterion as in CheckMate 142, but CONFIRM 2 also included patients with ECOG 0-2, with 5.1% of patients having an ECOG PS of 2.

NO16967[48] is a relevant alternative to CONFIRM 2 for the comparison with FOLFOX. NO16967 is a large (314 patients randomised to FOLFOX), open label RCT aiming to demonstrate noninferiority of XELOX versus FOLFOX-4 as second-line therapy in patients with mCRC after prior irinotecan-based chemotherapy. Similar to CONFIRM 2 and CheckMate 142, patients enrolled in NO16967 had measurable disease at baseline.

CAPRI-GOIM[49] is an open label, phase II, multicentre, Italian RCT selected as the alternative data source with the best patient outcomes. It evaluates the efficacy of FOLFOX as second-line treatment of KRAS exon 2 wild-type mCRC patients treated in first line with FOLFIRI plus cetuximab. That is, this trial focuses solely on the KRAS wild-type population which in CheckMate 142 makes up around 60% of the trial population. 79 patients were randomised to FOLFOX in CAPRI-GOIM.

The ERG considers both CONFIRM 2 and NO16967 to be relevant studies to inform the comparison with FOLFIRI but content with the company's choice to use CONFIRM for the base case and NO16967 for the scenario analysis.

3.4.1.3   Trifluridine-tipiracil and BSC

The phase III **RECOURSE**[50] study was a multinational, double-blind, placebo-controlled RCT comparing TRI-TIP plus BSC with placebo plus BSC in patients with previously treated mCRC. Patients in RECOURSE had received at least two prior therapies (inclusive of adjuvant chemotherapies if tumour had recurred within 6 months after last administration) compared with CheckMate 142 in which around 23% of patients had only had one prior therapy. In addition, patients in RECOURSE were required to have had prior fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, i.e. all patients had prior bevacizumab.

The company has used subgroups of the trial based on geographic location; the trial took place in centres in Europe, USA, Australia and Japan with subgroup data available separately for Europe, USA and Japan. 271, 64 and 178 patients were included in the TRI-TIP arm and 132, 35 and 88 patients were included in the BSC arm of the EU, USA and Japanese subgroups, respectively. The company has used the EU subgroup for its base case and the USA subgroup for a scenario analysis. The Japanese subgroup was not used by the company because of the small proportion of Asian patients in CheckMate 142, but also because of the better outcomes of the Japanese subgroup. The ERG does not consider it appropriate to choose or dismiss a subgroup based on the results but acknowledge that race was listed as a potential prognostic factor by the company and the ERG's clinical experts. Therefore, the ERG considers it appropriate to focus on the EU subgroup for the base case in order to have the best overlap between the populations of CheckMate 142 and RECOURSE. The USA subgroup was small, and the ERG considers the scenario analyses for both TRI-TIP and BSC based on this subgroup of limited value.

The company also provided scenario analyses of NIVO+IPI versus TRI-TIP based on the **TERRA**[51] trial and versus BSC based on the **LUME-colon 1**[52] trial as these provided some of the better outcomes for each comparator respectively. **TERRA** is a double-blind, placebo-controlled, phase III RCT of TRI-TIP, conducted at 30 sites in China, the Republic of Korea, and Thailand. It provided one of the best absolute outcomes for TRI-TIP (one other study highlighted [study J003-10040030] had even better outcomes, but was slightly smaller and all Japanese) but as the trial was in an all Asian population

and therefore very limited overlap with Checkmate 142, the ERG considers the EU subgroup of RECOURSE more relevant.

LUME-colon 1 is a large phase III, international, placebo-controlled RCT assessing nintedanib plus BSC versus placebo plus BSC for the treatment of patients with mCRC refractory to standard therapies. The company's rationale for choosing RECOURSE over LUME-colon 1 was that LUME-colon 1 reflects slightly more treatment experienced patients and a clinical pathway that may not be relevant to the UK setting: over a third of patients received previous regorafenib and patients had also previously received TRI-TIP. The ERG has not been able to find information on these baseline characteristics for the individual subgroups of RECOURSE but notes that in the overall trial population 83% of patients on BSC had had three or more prior therapies compared with 77.5% in LUME-colon 1 and 40.4% in CheckMate 142. The proportion of patients with prior regorafenib was 20% in RECOURSE, 36.5% in LUME-colon 1 and 9.2% in CheckMate 142. However, prior regorafenib was not identified as a potential prognostic factor and although it is not available through routine commissioning in UK clinical practice, prior regorafenib does not impact on the economic model. The ERG therefore considers LUME-colon 1 a reasonable alternative to the EU subgroup of RECOURSE for BSC.

3.4.2 Estimation of mean survival

The mechanism of action is very different for immunotherapies like nivolumab and ipilimumab compared with conventional chemotherapies for mCRC. Therefore, NIVO+IPI gives a different PFS and OS hazard profile compared with the comparators of interest. With NIVO+IPI, the peak hazard of an event occurs at or very soon after treatment initiation, followed by a rapid decrease in hazard, whereas the hazard profile of chemotherapies tends to have a smoothly developing hazard profile. The constant proportional hazards (PHs) assumption is therefore unlikely to be justified for PFS or OS between NIVO+IPI and any of the comparators of interest. The relative effect between NIVO+IPI and the comparators should, therefore, not be estimated as a hazard ratio or any other effect measure reliant on PHs to hold. The company has, therefore, chosen to undertake comparisons of mean survival for NIVO+IPI and each comparator. The ERG agrees that the PHs assumption is unlikely to hold for comparisons of NIVO+IPI and the comparators specified as relevant to this appraisal, and therefore agrees with the company's approach of using mean survival to inform the MAICs and naïve comparisons.

Mean survival for NIVO+IPI and each comparator was independently estimated by extrapolation of the KM data using parametric survival curves and calculation of the area under the curve. The extrapolation was done differently for NIVO+IPI and the comparators in order to account for the different hazard profiles for NIVO+IPI and the comparators. The modelling of NIVO+IPI and the comparators are briefly described in the sections below and discussed in detail in Sections 4.2.6.1 and 4.2.6.2.

NIVO+IPI

The estimation of survival for NIVO+IPI was used to inform treatment effectiveness in the economic model but also within the MAIC to estimate the relative treatment effect versus each comparator, which was then applied within the model to estimate the efficacy of the comparator.

For NIVO+IPI the company used semi-parametric survival models with KM data up to 6.44 months followed by an exponential and log-logistic distribution for PFS and OS, respectively. This was adjusted for matched general population lifetable hazard of death using UK life tables.[53] These methods are described in more detail in the CS, Appendix L, Section 2.2 and critiqued in Section 4.2.7 and Section 4.2.6.1.4 of this report.

Based on feedback from the ERG's clinical experts and visual inspection of the PFS and OS KM curves, the effect of NIVO+IPI starts to become apparent at ██, as indicated by the company. At the clarification stage the company was, therefore, asked to test the KM cut-off point in sensitivity analysis in line with advice in NICE DSU TSD 21.[54] The company provided results using a 2.99-month KM cut-off for PFS and OS. As per the base case analysis, the company choose the exponential distribution as the best fitting distribution to inform the PFS extrapolation and the log-logistic distribution as the best fitting distribution to inform the OS extrapolation. At the clarification stage, the company was also asked to explore spline-based models for PFS (to better capture the ████████████ profile) and fully parametric models for OS (as a similar dramatic change in hazard at ████████████ is not seen in the OS curve as it is for PFS). The different modelling approaches for NIVO+IPI are discussed in detail in Section 4.2.6.1 but a summary of the results is presented in Table 17, below.

Compared to the company's preferred modelling approach, a 2.99-month KM cut-off reduced the mean PFS time from ████████████ to ████████████ and the mean OS time increased from ████████████ to ████████████. Also, the spline-based model for PFS (████████████) and a fully

parametric log-logistic model for OS (███████████) reduced the mean survival compared with the company's base case approach (Table 17). The ERG considers the semi-parametric extrapolation, with KM data up to 2.99 months, the most plausible for both PFS and OS. They represent the ████████████ hazard well and extend the amount of data that can be used to inform the long-term extrapolation. The spline-based model for PFS and the fully parametric model for OS had poorer statistical fits.

The company provided an economic model during the final round of clarification that linked alternative survival extrapolations in the economic analysis with the survival inputs in the MAIC. However, there are unexplained differences in the company's base case analysis regarding the mean PFS and OS estimates between the economic analysis and MAICs (see Table 31 in Section 4.2.6.2.1). The ERG considers these discrepancies to be another reason to prefer the unadjusted comparison (naïve comparison) as it is more transparent and unlikely to introduce any additional bias into the comparison due to the analysis undertaken.

The mean survival outcomes in Table 17 are taken from the economic models provided at the initial round of clarification.

Table 17. Mean NIVO+IPI survival outcomes obtained from different extrapolations

OS		PFS	
Model	**Mean* (years)**	**Model**	**Mean* (years)**
Company preferred modelling			
Piecewise model, 6.44 months KM data followed by Log-logistic distribution	███	Piecewise model, 6.44 months KM data followed by exponential distribution	███
Modelling options requested by the ERG			
Piecewise model, 2.99 months KM data followed by a Log-logistic distribution	███	Piecewise model, 2.99 months KM data followed by an exponential distribution	███
Fully parametric model, log logistic distribution	███	Spline-based model	███
Abbreviations: KM, Kaplan Meier; OS, overall survival; PFS, progression free survival			
*Taken from the economic models provided by the company, including all-cause mortality			

For the comparators, KM data for PFS and OS were digitised, and parametric extrapolations were derived to provide estimates of mean survival. The company explored standard parametric distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) to extrapolate the digitised KM data as outlined in the NICE DSU TSD 14.[55] To select an appropriate distribution for the extrapolation of each outcome, the company assessed the fit of each modelled curve against the KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics and visual inspection of the fit over the observed period.

The company expected the majority of deaths for patients on comparator therapies to be disease driven. However, to be consistent with NIVO+IPI, the models of the comparator therapies incorporated matched lifetable hazard of mortality. These methods are described in detail in the CS, Appendix L, Section 2.2. However, given that the KM data are largely complete for all comparators, the ERG expects this adjustment to have a minimal impact on comparator outcomes.

The company's choice of parametric models and the resulting mean PFS and mean OS for each of the comparator studies, which inform both the naïve comparisons and MAIC with NIVO+IPI, are reported in Table 18. The KM data for all the comparator trials are largely complete and the ERG agrees with the company's choice of parametric models for each of the trials.

For these studies, mean PFS was below 7 months for all comparators with FOLFIRI treatment and BSC leading to the longest and shortest mean PFS respectively. Mean OS ranged between 7 and 17 months.

Table 18. Summary of outcomes informing the comparison (adapted from CS, Appendix L, Table 30)

			OS		PFS	
Study	Intervention	N	Selected model	Mean months (95% CI)	Selected model	Mean months (95% CI)
CONFIRM2 *	FOLFOX	429	Lognormal	17.3 (15.8, 18.9)	Lognormal	5.5 (5.1, 5.9)
RAISE	FOLFIRI	536	Generalised gamma	16.2 (14.8, 18.5)	Lognormal	6.6 (6.1, 7.3)

VELOUR *		614	Generalised gamma	15.7 (14.5, 17.3)	Lognormal	6.8 (6.2, 7.5)
RECOURSE/ EUR *	BSC	132	Generalised gamma	7.2 (5.6, 12.1)	Log-logistic	1.8 (1.7, 2.0)
RECOURSE/ USA		35	Generalised gamma	8.1 (4.7, 29.2)	Log-logistic	1.9 (1.6, 2.3)
RECOURSE/ EUR *	TRI-TIP	271	Lognormal	10.4 (8.9, 12.4)	Generalised gamma	3.7 (3.2, 5.0)
RECOURSE/ USA		64	Lognormal	11.7 (8.1, 19.7)	Generalised gamma	3.6 (3.0, 5.5)
* Used in base case						

3.4.3 MAIC methods

In order to reduce bias for the comparison of treatment effects between NIVO+IPI and the relevant comparators, due to the imbalance in both prognostic factors and treatment effect modifiers, the company performed unanchored matching adjusted indirect comparisons (MAICs). MAICs enable comparison of the treatment, in this case NIVO+IPI, for which the company has access to individual patient data (IPD) with aggregate outcome data and patient characteristics available in published literature for each of the comparators. In short, IPD in the index trial (CheckMate 142) were reweighted so that the baseline characteristics matched the comparator cohort. This aims to provide an estimate of the outcomes that would have been observed should patients, equivalent to those in the comparator trial, have been treated with NIVO+IPI.

As described in the CS (Appendix L, Section 2.4.) and with additional details provided at the clarification stage, the stages of MAIC performed by the company were as follows:

- Following study selection for each comparator (described in Section 3.4.1), OS and PFS Kaplan-Meier data were digitised and parametric extrapolations were derived to provide estimates of mean survival (see Section 3.4.2).
- Mean outcomes for the comparator were converted to the log scale.
- Patients in the index study (CheckMate 142) who could not be present in the comparator study due to design (form overlap) were excluded. The company clarified that; patients in CheckMate 142 were assessed in reference to stated eligibility criteria for the comparator study; if patients would not have been eligible for the comparator study, then zero weight

would have been applied and those patients would not have informed subsequent outcomes. However, in the presented comparisons, no patients were specifically excluded.

- Form a series of weights using the method of moments such that each of the matched aggregate measures of prognostic variables in the comparator trial is equalled by the weighted aggregate measure in the index study.

- Apply these weights to the outcomes in the index study.

- Mean outcomes from the adjusted NIVO+IPI arm (i.e. MAIC output) were converted to the log scale.

- The difference in log mean between the adjusted or reweighted index study and the comparator study was calculated.

- The relative treatment effect (the difference in log mean) was applied to the unadjusted NIVO+IPI log mean outcome to derive an adjusted log mean for the comparator. The difference in log mean outcomes was applied directly within the economic model.

MAICs lead to an adjustment of the index data, in this case CheckMate 142, so that it reflects the effect of NIVO+IPI had it been used in a population like that of the comparator trial. In order to calculate the treatment effect of the comparators in the CheckMate 142 population, in the last step of the MAIC the company applies the relative treatment effect to the unadjusted CheckMate 142 data. That is, the company transposed the relative treatment effect onto the population of interest; the MSI-H/dMMR mCRC population of the unadjusted CheckMate 142. A difference in relative treatment effect can be projected into any population if the *shared effect modifier assumption* is fulfilled.[43] However, as stated in NICE DSU TSD 18,[43] the shared effect modifier assumption is evaluated on a clinical and biological basis where, e.g. treatments in the same class (i.e. sharing biological properties or mode of action) are likely to satisfy the assumption, and those from different classes are not. This is thus a very strong assumption to make for the comparison of immunotherapies like NIVO+IPI and conventional chemotherapies. The ERG notes that transposing the relative treatment effect onto the unadjusted CheckMate 142 may introduce an unknown amount of bias. However, the ERG considers it not to be an unreasonable assumption in order to assess the relative clinical and cost effectiveness of NIVO+IPI in the population of interest.

3.4.3.1 Identification and selection of covariates

The company determined potential matching variables by consultation with clinical experts and with reference to the availability of aggregate data from comparator studies. The variables considered in the CS were:

- Age (years);
- Sex;
- Geographic region;
- Lynch syndrome (per clinical advice, expected to be confounded with age and not independently prognostic);
- KRAS/BRAF mutation status;
- Baseline ECOG performance status;
- Time from initial diagnosis to first dose;
- Primary tumour location;
- Number of prior systemic regimens received;
- Time from completion of most recent prior regimen to treatment (per clinical advice, this was expected to be more relevant than time from initial diagnosis);
- Time from progression upon most recent prior therapy regimen to treatment.

At the clarification stage the company added the following to the list of covariates:

- Race;
- Metastases location;
- Number of metastatic sites.

Of the initial list of variables, the ERG's clinical experts agree that these are all prognostic factors for mCRC. Of these, the most important factors are age, BRAF/KRAS mutation status, ECOG performance status, primary tumour location and number of prior regimens. A worse prognosis is associated with higher age, higher ECOG performance status, larger number of prior regimens, and primary tumours on the right side of the colon. The ERG's clinical experts clarified that tumours on the right side are more likely to have dMMR/MSI-H and, therefore, are more likely to have a worse prognosis.

Lynch syndrome, BRAF mutation status, and time from progression upon most recent prior therapy regimen to treatment were not reported for any of the comparator studies. As such, these variables did not feature in the selection. In addition, primary tumour location was inconsistently coded between studies: consistent distinction was only made between rectal tumours and colon tumours. Thus, only the primary tumour location of "rectum", exclusive of all other sites, was compared for matching. The ERG's clinical experts informed that a divide of rectum and all other sites for primary tumour location is unhelpful as it does not distinguish between primary tumours on the left and right side of the colon, which is more strongly linked to prognosis.

From the list of prognostic factors, three covariate sets were initially determined by the company:

- **Primary: Predictive + demographic** – A subset of available variables identified by a forward stepwise selection process for each comparator, plus age and sex (described in the CS, Appendix L, Section 2.4.4.). This was chosen to optimise bias reduction among the observed variables without incurring precision losses due to adjustment for variables that were considered not to materially affect the outcome estimate.
- **Fallback: Demographic** – Age and sex alone, providing a fallback model when small subgroups within CheckMate 142 were over-represented in the comparator study, resulting in a concentration of MAIC weights in patients with the subgroup inclusion characteristic.
- **All** – All available prognostic factors of the above defined list. The "All" adjustment set weighting was performed to demonstrate the accumulated effect of all potential prognostic variables.

At the clarification stage the company defined an additional covariate set:

- **Secondary:** as per the primary adjustment set, but removal of 1) proportion of patients specified as Asian, and 2) proportion of patients where primary tumour location is specified as rectum.

Adjustment for differences in baseline covariates reduces bias but also decreases the effective sample size and so increases the variance of the outcome estimates. The company states that for covariates that do not correlate with the outcome in CheckMate 142, adjustment does not affect bias and so was avoided to prevent unnecessary inflation of variance. Covariates observed to modify the outcomes within CheckMate 142 were identified by a forward stepwise selection process (Primary covariate set). The company also states that prognostic variables that are expected to

modify outcomes in the comparator trial and which may be imbalanced between the trials but are not conditionally correlated with outcome in CheckMate 142, they will not bias the outcome estimates. These variables were therefore preferentially excluded.

The ERG reiterates the recommendation in TSD 18 that unanchored MAICs requires all effect modifiers and prognostic variables to be adjusted for, i.e. not limiting adjustment to covariates identified through a forward stepwise selection process (Primary covariate set) or an even smaller and selection of covariates, such as the Fallback set, in order to maintain a lower variance. A fully adjusted unanchored MAIC will be more uncertain but also more accurate (smaller systematic error) than analyses using the limited covariate sets suggested by the company. The ERG therefore considers the fully adjusted (All available covariates) analyses the most appropriate for the MAIC. However, the ERG notes that although bias is minimised by adjusting for all reported prognostic differences and effect modifiers, unanchored MAICs will always be subject to unknown amounts of residual bias due to unobserved prognostic variables and effect modifiers.

3.4.3.2   Evidence of bias reduction

The company calculated the magnitude of potential bias reduction compared with a standard indirect comparison by multiplying the cox linear interaction coefficient by the difference in means. DSU TSD 18[43] recommends that for anchored MAICs the evidence for effect modifier status should be given, along with the proposed size of the interaction effect and the imbalance between the study populations, as presented by the company. However, as the MAICs in this appraisal are unanchored, the ERG highlights that all effect modifiers as well as all potential prognostic factors should be adjusted for in order to minimise bias. The company's estimate of bias reduction is therefore not of relevance for this appraisal.

3.4.3.3   Estimation of systematic error

A naïve or unadjusted indirect comparison will include sampling error plus systematic error due to the imbalance in both prognostic factors and effect modifiers. On top of differences in patient characteristics, there are also likely to be differences in study design and study conduct which may introduce heterogeneity in the results, but which can't be adjusted for within an MAIC. The size of the systematic error may be reduced by appropriate use of MAIC. Unaccounted for factors are minimised by adjusting for all prognostic differences and effect modifiers, but some will always

remain. It is therefore essential to provide evidence on the likely extent of error due to unaccounted for covariates, in relation to the observed relative treatment effect.

DSU TSD 18[43] recommends that the systematic error be assessed by identifying a set of external studies in the target population with aggregate data on the relevant outcome. Then carry out a random-effects pooling across absolute outcomes on study arms in the target population, controlling for treatment. Predicted outcomes on the treatment, in this case NIVO+IPI, in each of the study arms used in the pooling can be obtained using MAIC, and a similar pooling performed. If all prognostic variables and effect modifiers are accounted for, then the between-studies variation of the predicted outcomes will match that of the observed outcomes (that is, residual variation will be minimised). However, lower between-studies variation of predicted outcomes would be expected if some prognostic variables and/or effect modifiers remain unaccounted for. The ratio of the between-studies variance in predicted to observed outcomes, could be interpreted as the proportion of systematic error "explained" by the included covariates.

The company could potentially use the NIVO+IPI studies NIPICOL[36] and Lam 2020[37], which are both in the target population (MSI-H/dMMR mCRC), in order to estimate the likely extent of error due to unaccounted for covariates. However, both studies may be too small and data too immature to be informative. Due to the paucity of data in the target population, the company can't reliably show that a MAIC provides a reduction in bias compared with a naïve comparison. The accuracy of the resulting estimates is, therefore, entirely unknown, as there is no estimate of the potential magnitude of residual bias. The ERG considers this another reason for the naïve comparisons between NIVO+IPI and the comparators to be the most appropriate.

3.4.4 MAIC results

3.4.4.1 Company base case MAIC results

The company's MAIC results informing their base case and scenario analyses are presented in Table 19 for PFS and Table 20 for OS, below. These include the MAIC results presented in the CS for the company's preferred covariate set, and results in response to clarification based on an updated selection of covariates either adjusting for a limited covariate set or adjusted for all available covariates. The MAICs are based on the company's preferred modelling of NIVO+IPI; a semi-parametric relative survival model of NIVO+IPI, incorporating KM data up to month 6.44, followed by an exponential distribution.

Choice of comparator study generally has a relatively minor impact on outcomes. Similarly, the ERG agrees with the company that the result of using the fallback, primary or secondary covariate sets are generally similar to the unadjusted data. For most comparators the adjustment led to a longer or slightly longer PFS and OS. Adjusting for all available covariates, however, as recommended for unanchored comparisons, had a large impact on the effective sample size (ESS), which is less than 20 for all comparator studies, and in some cases leads to a considerably longer mean survival.[43] For FOLFIRI, mean OS when adjusting for all available covariates was 31.8 months based on the VELOUR trial compared with 15.7 months before adjustment, which the ERG's clinical experts agrees with the company, lacks clinical plausibility. For the MAICs for TRI-TIP and BSC, which are informed by the RECOURSE trial, the ESS reduced to zero when adjusting for all available covariates and output for these analyses could not be provided.

The company concludes that adjusting for all available covariates results in spurious results that lack clinical plausibility or face validity. The ERG agrees that the low ESS indicates high concentration of patient weights in few individuals, and notes that this indicates that there is very little overlap between the target and index population which highlights the large uncertainty around these estimates. The ERG also notes that, although partially adjusted MAICs may provide more plausible results, both partially and fully adjusted analyses are biased, although the fully adjusted probably less so. In addition, these results are all based on the company's preferred modelling of NIVO+IPI. MAIC results based on the modelling of NIVO+IPI preferred by the ERG are presented in the next section.

Due to the substantial limitations of the possible adjustments for the MAICs, the ERG considers it more appropriate to use the naïve comparisons of NIVO+IPI and the comparators. However, the low effective sample size of the MAICs adjusting for all reported covariates gives an indication of how different the study populations potentially are. When interpreting the results of the naïve comparisons the substantial differences between the study populations and the resulting uncertainty around the relative efficacy of NIVO+IPI versus each of the comparators, therefore needs to be kept in mind.

Table 19. Summary of progression-free survival outcomes from MAIC analyses (adapted from additional clarification response Table 7)

Comparator	Study	Unadjusted study		Company submission MAIC			A11* MAIC analysis (limited covariates)			A12* MAIC analysis (all available covariates)		
		Study size	Mean survival outcomes (months)	ESS	Covariate set	Mean survival outcomes (months)	ESS	Covariate set	Mean survival outcomes (months)	ESS	Covariate set	Mean survival outcomes (months)
NIVO+IPI	CheckMate 142	119	■■■									
FOLFOX	CONFIRM2	429	5.47	75.9	Primary	4.49	21.4	Primary	5.94	18.6	All	5.02
	NO16967	314	5.36	NA	NA	NA	108.2	Secondary	5.45	12.8	All	11.68
	CAPRI-GOIM	79	6.7	NA	NA	NA	98.6	Secondary	7	6.4	All	18.7
FOLFIRI	RAISE	536	6.62	98.4	Fallback	7.54	91.1	Secondary	7.86	8.8	All	12.42
	VELOUR	614	6.79	96.8	Fallback	6.33	57.4	Secondary	9.66	17.5	All	11.56
	NCT01479465	80	8.17	NA	NA	NA	19.7	Primary	10.34	18.2	All	10.85
Trifluridine/tipiracil	RECOURSE/EUR	271	3.68	96.5	Fallback	4.19	63.2	Secondary	4.29	NA	All	NA
	RECOURSE/USA	64	3.63	106	Fallback	3.7	33.5	Secondary	3.38	NA	All	NA
	TERRA	271	3.99	NA	NA	NA	92.5	Secondary	3.35	5.7	All	6.81

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Best supportive care	RECOURSE/ EUR	132	1.83	97.5	Fallback	2.1	64.2	Secondary	2.14	NA	All	NA
	RECOURSE/ USA	35	1.87	106.4	Fallback	1.9	36.1	Secondary	1.67	NA	All	NA
	LUMECOLON 1	382	1.88	NA	NA	NA	79.5	Secondary	2.12	4.4	All	1.76
	TERRA	135	1.97	NA	NA	NA	85.1	Secondary	1.58	13	All	2.11

*Reported in response to clarification question A11 and A12

Abbreviations: ESS, effective sample size; MAIC, matching adjusted indirect comparison

Table 20. Summary of overall survival outcomes from MAIC analyses (adapted from additional clarification response Table 6)

Comparator	Study	Unadjusted study		Company submission MAIC			A11 MAIC analysis (limited covariates)			A12 MAIC analysis (all available covariates)		
		Study size	Mean survival outcomes (months)	ESS	Covariate set	Mean survival outcomes (months)	ESS	Covariate set	Mean survival outcomes (months)	ESS	Covariate set	Mean survival outcomes (months)
NIVO+IPI	CheckMate 142	119	■									
FOLFOX	CONFIRM2	429	17.3	75.9	Primary	15.65	21.4	Primary	14.5	18.6	All	16.8
	NO16967	314	14.0	NA	NA	NA	108.2	Secondary	13.5	12.8	All	14.4
	CAPRI-GOIM	79	21.2	NA	NA	NA	98.6	Secondary	21.8	6.4	All	36.6

FOLFIRI	RAISE	536	16.2	98.4	Fallback	17.19	91.1	Secondary	18.9	8.8	All	22.7
	VELOUR	614	15.7	96.8	Fallback	15.3	57.4	Secondary	21.9	17.5	All	31.8
	NCT0147946 5	80	21.0	NA	NA	NA	19.7	Primary	41.4	18.2	All	38.9
Trifluridine/ tipiracil	RECOURSE /EUR	271	10.4	96.5	Fallback	10.86	63.2	Secondary	15.4	NA	All	NA
	RECOURSE /USA	64	11.7	106	Fallback	11.7	33.5	Secondary	12.1	NA	All	NA
	TERRA	271	11.6	NA	NA	NA	92.5	Secondary	8.5	5.7	All	32.2
Best supportive care	RECOURSE /EUR	132	7.2	97.5	Fallback	7.55	64.2	Secondary	10.8	NA	All	NA
	RECOURSE /USA	35	8.1	106.4	Fallback	8.13	36.1	Secondary	7.3	NA	All	NA
	LUMECOLO N1	382	10.2	NA	NA	NA	79.5	Secondary	9.5	4.4	All	12.2
	TERRA	135	8.7	NA	NA	NA	85.1	Secondary	6.2	13.0	All	9.9

*Reported in response to clarification question A11 and A12

Abbreviations: ESS, effective sample size; MAIC, matching adjusted indirect comparison

The company provided results for the MAIC based on alternative modelling of NIVO+IPI, requested by the ERG at the clarification stage:

- PFS:
    - piecewise model, KM to 2.99 months followed by an exponential distribution;
    - spline-based model.
- OS:
    - piecewise model, KM to 2.99 months followed by a log logistic distribution;
    - fully parametric model, log logistic distribution.

The different modelling approaches for NIVO+IPI are discussed in detail in Section 4.2.6. Though, the ERG considers the piecewise modelling, with KM data up to 2.99 months, the most plausible for both PFS and OS. The results of the MAICs based on piecewise model were provided both for the fully adjusted (all available covariates) and partially adjusted (limited covariates) for PFS (Table 21) and OS (Table 22).

The MAICs using the ERG preferred modelling of NIVO+IPI gave similar results to the company's preferred modelling of NIVO+IPI in that:

- choice of comparator study generally had a relatively minor impact on outcomes;
- results of partial covariate adjustment were similar to the unadjusted data;
- for most comparators the adjustment led to a longer mean PFS and OS;
- adjusting for all available covariates led to an ESS of less than 20 for all comparator studies, and in some cases a considerably longer mean survival.

As concluded in the previous section, the ERG considers the most appropriate analyses the naïve comparisons of NIVO+IPI and the comparators. However, when interpreting the results of the naïve comparisons, the results of the MAICs adjusting for all reported covariates should be kept in mind.

Table 21. Summary of comparator progression-free survival outcomes from MAIC analyses based on ERG's preferred modelling of NIVO+IPI (PFS 2.99 months KM data + exponential)

Comparator	Study	Unadjusted study		A11 MAIC analysis (limited covariates)			A12 MAIC analysis (all available covariates)		
		Study size	Mean progression-free survival (months)	ESS	Covariate set	Mean progression-free survival (months)	ESS	Covariate set	Mean progression-free survival (months)
FOLFOX	CONFIRM2	429	5.47	21.4	Primary	7.08	18.6	All	6.82
	NO16967	314	5.36	108.2	Secondary	5.40	12.8	All	10.85
	CAPRI-GOIM	79	6.7	98.6	Secondary	6.63	6.4	All	15.63
FOLFIRI	RAISE	536	6.62	91.1	Secondary	7.36	8.8	All	11.59
	VELOUR	614	6.79	57.4	Secondary	9.65	17.5	All	15.30
	NCT01479465	80	8.17	19.7	Primary	11.86	18.2	All	11.63
Trifluridine/ tipiracil	RECOURSE/EUR	271	3.68	63.2	Secondary	3.83	NA	All	NA
	RECOURSE/USA	64	3.63	33.5	Secondary	3.84	NA	All	NA
	TERRA	271	3.99	92.5	Secondary	3.43	5.7	All	5.89
Best supportive care	RECOURSE/EUR	132	1.83	64.2	Secondary	1.92	NA	All	NA
	RECOURSE/USA	35	1.87	36.1	Secondary	1.87	NA	All	NA

Comparator	Study	Study size	Mean overall survival (months)	ESS	Covariate set	Mean overall survival (months)	ESS	Covariate set	Mean overall survival (months)
	LUMECOLON1	382	1.88	79.5	Secondary	2.09	4.4	All	4.13
	TERRA	135	1.97	85.1	Secondary	1.68	13	All	2.43

Table 22. Summary of comparator overall survival outcomes from MAIC analyses based on ERG's preferred modelling of NIVO+IPI (OS 2.99 months KM data + log logistic)

Comparator	Study	Unadjusted study		MAIC analysis (limited covariates)			MAIC analysis (all available covariates)		
		Study size	Mean overall survival (months)	ESS	Covariate set	Mean overall survival (months)	ESS	Covariate set	Mean overall survival (months)
FOLFOX	CONFIRM2	429	17.3	21.4	Primary	18.13	18.6	All	18.29
	NO16967	314	14.0	108.2	Secondary	14.47	12.8	All	21.13
	CAPRI-GOIM	79	21.2	98.6	Secondary	23.37	6.4	All	64.84
FOLFIRI	RAISE	536	16.2	91.1	Secondary	19.74	8.8	All	34.09
	VELOUR	614	15.7	57.4	Secondary	27.77	17.5	All	38.52
	NCT01479465	80	21.0	19.7	Primary	42.60	18.2	All	38.98
Trifluridine/ tipiracil	RECOURSE/EUR	271	10.4	63.2	Secondary	11.92	NA	All	NA
	RECOURSE/USA	64	11.7	33.5	Secondary	15.17	NA	All	NA
	TERRA	271	11.6	92.5	Secondary	8.94	5.7	All	29.74

	RECOURSE/EUR	132	7.2	64.2	Secondary	8.17	NA	All	NA
Best supportive care	RECOURSE/USA	35	8.1	36.1	Secondary	9.12	NA	All	NA
	LUMECOLON1	382	10.2	79.5	Secondary	9.87	4.4	All	14.29
	TERRA	135	8.7	85.1	Secondary	6.50	13.0	All	8.36

3.5 Conclusions of the clinical effectiveness section

3.5.1 CheckMate 142 – NIVO+IPI

The key trial assessing NIVO+IPI is CheckMate 142, a phase II, non-comparative, open-label trial. The 119 patients enrolled in the cohort of CheckMate 142 who were given NIVO+IPI had mCRC assessed as dMMR and/or MSI-H, and disease progression following ≥1 prior treatment(s), which must include a fluoropyrimidine-based combination chemotherapy. Most patients will be given either FOLFOX or FOLFIRI as first line therapy for mCRC in UK clinical practice. The ERG's clinical experts consider the prior therapies of the population enrolled in CheckMate 142, as well as other patient characteristics, to be representative of patients in England likely to be eligible for treatment with NIVO+IPI.

In CheckMate 142, nivolumab was given at a dose of 3mg/kg together with ipilimumab at 1mg/kg every 3 weeks for 4 doses followed by nivolumab monotherapy 3mg/kg every 2 weeks. The anticipated market authorisation specifies a fixed dose of nivolumab of 240mg every 2 weeks. The ERG's clinical experts commented that the two dosing schedules for nivolumab are expected to be of equivalent clinical effectiveness.

Patients in CheckMate 142 continued nivolumab therapy until disease progression or unacceptable toxicity, whereas the draft Summary of Product Characteristics (SmPC) recommends that nivolumab therapy is continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. This means that treatment may be continued beyond progression if a patient is deemed to still derive a clinical benefit or discontinued prior to progression in patients with limited clinical benefit. In the economic model the company has applied a stopping rule at 2 years for nivolumab (base case analysis) and provided a scenario analysis where no stopping rule is applied. In CheckMate 142 no formal stopping rule was used for nivolumab but a protocol amendment in Feb 2019 included an optional stopping point at 2 years for patients assessed as having achieved maximum clinical benefit at this stage. The company highlights that in other indications a stopping rule at 2 years is frequently applied for nivolumab and, according to the company's clinical experts, it is considered clinical practice in the treatment of mCRC. The ERG's clinical experts fed back that their preference would be to continue nivolumab treatment until disease progression and not to take patients off nivolumab treatment if they are still deriving a benefit and remain progression-free at 2 years.

At a median follow-up ███ months, NIVO+IPI therapy demonstrated a clinically meaningful effect on outcomes including ORR, PFS and OS. Investigator assessed ORR was ████████████████. Median progression-free survival (PFS) was ████ months per IA and ████ months per BICR. Median overall survival (OS) ██████████████████████. The 12-month, and 24-month event-free rates were 84.9% and ████ for OS, respectively, and 71.6% and ████, for PFS, respectively. The ERG's clinical experts commented that similar results have never been seen before for this patient population, which they consider having a very poor prognosis. However, the ERG notes that results tend to be better in open label, single arm trials than in double blind RCTs. This means that the results of CheckMate 142, as a relatively small single arm study, may show quite different absolute results than would be expected if it had been a double blind RCT or what would be expected in UK clinical practice.

3.5.2 ITC of NIVO+IPI versus relevant comparators

The ERG considers the company's search strategies to be inconsistent and lacking comprehensiveness. This leads to uncertainty in whether all relevant studies have been captured and, as a consequence, further uncertainty in the choice of studies informing the indirect comparisons with CheckMate 142. However, of the studies included in the review, the ERG broadly agrees with the company's choice of individual studies for the indirect comparisons. Unlike CheckMate 142, the selected comparator studies were all RCTs and all in the mCRC population where MSI-H/dMMR status either wasn't reported, or only a very small proportion of patients had MSI-H/dMMR mCRC.

The company used mean survival as the effect measure for the MAICs and naïve comparisons. Mean survival for NIVO+IPI and each comparator was independently estimated by extrapolation of the KM data using standard parametric survival curves and calculation of the area under the curve. The ERG agrees with the company's choice of parametric model for each of the comparator trials.

For NIVO+IPI, the company estimated mean survival using piecewise modelling with KM data up to 6.44 months followed by extrapolation of the KM data using standard parametric survival curves. The ERG requested alternative modelling approaches for NIVO+IPI and found piecewise modelling with KM data up to 2.99 months the most plausible for both PFS and OS. Using the company's preferred modelling approach mean PFS was ██████████ and mean OS ██████████ for patients treated with NIVO+IPI in CheckMate 142. Compared to the company's preferred modelling approach, a 2.99-month KM cut-off reduced the mean PFS time to ██████████, and increased the

mean OS time to ████████. In contrast, from the selection of RCTs presented, the longest mean PFS for the comparators was for FOLFIRI at 6.8 months and the longest OS was for FOLFOX at 17.3 months. However, a naïve comparison of these survival estimates will be biased due to imbalances in observed and unobserved prognostic factors and effect modifiers between the study populations. In order to reduce this bias, the company performed MAICs adjusting either for a select set of covariates (partially adjusted, company's preferred option) or for all reported covariates (fully adjusted). For unanchored MAICs, it is recommended that all available effect modifiers and prognostic variables be adjusted for in order to minimise bias and more reliably predict outcomes. Therefore, of the different adjusted analyses presented by the company, the ERG considers the MAIC adjusted for all available covariates to provide the most accurate results, although the imprecision is very large, and the results are potentially unreliable as they are based on a low effective sample size. The ERG's preferred approach is therefore the use of a naïve comparison as it is transparent in terms of the likely biases that exist within the comparison and the analysis itself has not introduced additional bias into the comparison.

Irrespective of the analysis used, and despite survival data being immature, the available evidence shows that treatment with NIVO+IPI leads to substantial absolute benefits in terms of both PFS and OS. However, the ERG highlights that there is an unquantifiable but likely very large amount of uncertainty around all the results presented, both adjusted and unadjusted, due to residual bias and differences that haven't or can't be adjusted for.

Some of these uncertainties will likely be resolved with longer follow up of CheckMate 142, but more importantly by the reporting of CheckMate 8HW, a phase III RCT, which will provide comparative efficacy of NIVO+IPI versus the current standard of care in patients with MSI-H/dMMR mCRC who have received at least one prior line of systemic therapy. CheckMate 8HW is ongoing with an estimated primary completion date in 2025.[38] However, preliminary results are expected in ████████.

4 Cost effectiveness

The company's deterministic base case results are summarised in Table 23.

Table 23. Company's deterministic base case results

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■■	■■	■■	-	-	-	-
TRI-TIP	16,978	0.915	0.630	■■	■■	■■	£13,367
Comparison B							
NIVO+IPI	■■	■■	■■	-	-	-	-
BSC	9,379	0.639	0.441	■■	■■	■■	£14,211
Comparison C							
NIVO+IPI	■■	■■	■■	-	-	-	-
FOLFOX	12,176	1.314	0.884	■■	■■	■■	£14,839
Comparison D							
NIVO+IPI	■■	■■	■■	-	-	-	-
FOLFIRI	11,527	1.284	0.874	■■	■■	■■	£14,930

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

4.1 ERG comment on the company's review of cost effectiveness evidence

The company performed three systematic literature reviews (SLRs) to identify published studies that could inform the cost-effectiveness evaluation of NIVO+IPI. These SLRs covered the cost-effectiveness evidence, the health-related quality of life (HRQoL) evidence and the costs and resource use evidence associated with recurrent, relapsed, progressed or metastatic colorectal cancer (mCRC). The company did not expect to find evidence for the mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) subgroups, so their search strategies were designed with a focus on the wider disease area. Searches were initially run in January 2017 and

were last updated in August 2020. A summary of the Evidence Review Group's (ERG) critique of the company's SLR is given in Table 24. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 24. Systematic Literature Review summary

| Systematic review step | Section of CS in which methods are reported | | | ERG assessment of robustness of methods |
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G	Appendix H	Appendix I	Appropriate. Electronic databases included: EMBASE, Medline, Medline (R) In-Process, The Cochrane Library and EconLit. Other sources for "grey" literature included: HTA websites (NICE, SMC, AWMSG, CADTH and PBAC) and conference proceedings (ASCO, ESMO and GCS). Search filters were adopted from previously used filters, CRD filters and those used in other HTA publications.
Inclusion/exclusion criteria	Appendix G	Appendix H	Appendix I	Appropriate. A publication restriction was implemented during the initial review period to exclude studies published prior to 2004.
Screening	Appendix G	Appendix H	Appendix I	Appropriate.
Data extraction	Appendix G	Appendix H	Appendix I	Appropriate. Due to the high volume of relevant cost-effectiveness evidence, the company could have restricted extractions to those in a UK setting or those using a CUA study design.
Quality assessment of included studies	Appendix G using the Drummond checklist[56]	No QA checklist completed	-	Appropriate. Cost and resource use studies also included and assessed as cost-effectiveness studies. Checklists such as CASP (recommended in DSU TSD 9[57]) would be preferred for HRQoL evidence.

Abbreviations: ASCO, American Society for Clinical Oncology; AWMSG, All Wales Medicines Strategy Group; CASP, Critical Appraisal Skills Programme; CADTH, Canadian Agency for Drugs and Technologies in Health; CRD, Centre for

Overall, a total of 101 cost-effectiveness studies, 34 HRQoL studies and 15 cost and resource use studies were included by the company. None of these studies were used for parameterising the model and the NICE appraisal of TRI-TIP for previously treated metastatic colorectal cancer (TA405)[2] was not included by the company. However, the ERG does not consider this to be a major issue as the company employed NICE TA405 and other appropriate sources of evidence in the model. These were predominantly the CheckMate 142 trial, the NHS Reference Cost Schedule[58] and the PSSRU Unit Costs of Health and Social Care[59].

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 25 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist[60] for the base-case analysis, with reference to the NICE final scope[28] outlined in Section 2.

Table 25. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes.
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company provided a cost-utility analysis with pairwise results. The ERG has calculated fully incremental results in Table 40.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes (lifetime horizon).
Synthesis of evidence on health effects	Based on systematic review	The company undertook a systematic review, but other sources of evidence were used to inform the model. The ERG

		agrees with the company that these other sources are appropriate.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes (QALYs based on EQ-5D-3L data from CheckMate 142 and CORRECT[1] used in the base case analysis).
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes (costs have been sourced using NHS reference costs[58], the PSSRU Unit Costs of Health and Social Care[59], eMIT[61] and published literature and are reported in pounds sterling for a 2018/19 cost year).
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.

Abbreviations: ERG, evidence review group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

4.2.2   Population

The economic analysis considers the use of NIVO+IPI for the

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████████████████████████████, in line with the anticipated marketing authorisation. The key trial assessing NIVO+IPI in this indication is CheckMate 142, a phase II, non-comparative, open-label trial. The baseline characteristics in the model are derived from the subgroup of patients enrolled in this trial that received NIVO+IPI (cStage arm) and include age (56.6 years), proportion male (58.8%) and body weight (73.7kg). As shown in the company's one-way sensitivity analysis, cost-effectiveness results are sensitive to the age of patients (see Section 5.1.2.2).

As described in Section 2, most patients will be given either FOLFOX or FOLFIRI as first line therapy for mCRC in UK clinical practice. However, patients in CheckMate 142 were heavily pre-treated even though NIVO+IPI is most likely to be used at second line. Given that the effectiveness of NIVO+IPI is likely to reduce at later treatment lines, the cost-effectiveness results are likely to be conservative compared with what could be expected if all patients in CheckMate 142 received NIVO+IPI at second line. The ERG also adds that subgroups looking at second line and third or later lines were not requested from the company due to the small number of patients in these subgroups.

All comparator studies were in the mCRC population whereby MSI-H/dMMR status either wasn't reported, or only a very small proportion of patients had MSI-H/dMMR mCRC. As has been highlighted by the company in the CS, the prognosis of patients with mCRC population and MSI-H/dMMR seems to have a worse prognosis than the overall mCRC population, which the ERG's clinical expert agree with.

However, the ERG considers it important to add that as MSI-H/dMMR constitute a small subgroup of patients with mCRC, the evidence is sparse. It is therefore unclear what treatment modifying effect that MSI-H/dMMR status has on NIVO+IPI as well as the different comparators. As such, clinical expert opinion is the only basis the ERG has to indicate that the cost-effectiveness results may be conservative.

4.2.3   Interventions and comparators

The intervention considered for the economic analysis is NIVO+IPI, both are given as intravenous infusions. The SmPC for NIVO+IPI specifies that treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient[62]. During CheckMate 142, patients could continue nivolumab post progression at the discretion of the clinician. As such, the time on treatment (ToT) and PFS curves can cross in the economic analysis. The company also applied a 2-year stopping rule to nivolumab in their base case analysis even though no formal stopping rule was applied during CheckMate 142 or is expected to be in the marketing authorisation. More information and critique of the methods used to estimate proportions of patients on treatment within each health state is provided in Section 4.2.6.1.2.

The ERG also notes that there is a small discrepancy between the nivolumab maintenance dose received in CheckMate 142 and included in anticipated marketing authorisation. Patients enrolled in CheckMate 142 received nivolumab 3 mg/kg IV once every 2 weeks. This equates to 221.1 mg

assuming body weight of 73.7 kg, based on mean weight in CheckMate 142. The dosage included in the anticipated market authorisation, is a fixed dose of 240mg every 2 weeks. However, as nivolumab vials provide a dose of 240mg, it is assumed that the remainder of each vial is wasted in the economic analysis. As such, there is no discrepancy in terms of treatment costs. The ERG's clinical experts also advised that the two dosing schedules for nivolumab would be of equivalent clinical effectiveness (see Section 2.3.2).

The key comparators included in company's economic analysis are:

- Folinic acid plus fluorouracil plus irinotecan (FOLFIRI);
- Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX);
- Trifluridine-tipiracil (TRI-TIP); and,
- Best supportive care (BSC).

In the NICE final scope[28], single agent irinotecan and raltitrexed were also listed as relevant comparators. The company's clinical experts stated these treatments are rarely used in clinical practice (<5% patients). Nonetheless, the company presented cost-effectiveness results for these comparators in order to comply with the NICE final scope. Based on advice from the ERG's clinical experts, the company's rationale to exclude single agent irinotecan and raltitrexed as key comparators is considered reasonable by the ERG. As such, these comparators are not discussed further in this report.

The treatment regimens included in the economic analysis are summarised in Table 26. For FOLFIRI and FOLFOX these were taken from the most frequent regimen reported in the SLR. As for TRI-TIP, the treatment regimen was taken from the SmPC[63]. Treatment acquisition costs and administration costs are given in Section 4.2.10.1.

Table 26. Treatment regimens included in the model

Regimen	Components	Dosing instructions	Treatment cycle
NIVO+IPI	NIVO	3mg/kg by intravenous infusion over 30 mins every 3 weeks for 4 doses and then 240mg every 2 weeks thereafter	
	IPI	1mg/kg by intravenous infusion over 90 mins every 3 weeks for 4 doses	
TRI-TIP		35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle	Once every 28 days

Regimen	Components	Dosing instructions	Treatment cycle
FOLFIRI	Fluorouracil (bolus)	400 mg/m^2 bolus on day 1	Once every 14 days
	Fluorouracil (IV)	2,400 mg/m^2 infusion over 46 hours	
	Folinic acid	200 mg/m^2 infusion	
	Irinotecan	180 mg/m^2 intravenous infusion	
FOLFOX	Fluorouracil (bolus)	400 mg/m^2 bolus on day 1	Once every 14 days
	Fluorouracil (IV)	2,400 mg/m^2 infusion over 46 hours	
	Folinic acid	200 mg/m^2 infusion	
	Oxaliplatin	100 mg/m^2 infusion	

Abbreviations: FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; IPI, ipilumab; IV, intravenous; NIVO, nivolumab; TRI-TIP, Trifluridine/tipiracil

4.2.4   Modelling approach and model structure

The company developed a *de novo* model in Microsoft Excel®. The model is based on a partitioned survival analysis structure, with three main health states: pre-progression, post-progression and death. The pre-progression health state is sub-divided into pre-progression on 2nd line treatment and pre-progression off 2nd line treatment, with proportions determined by ToT data. The post-progression health state is also sub-divided into post-progression on 2nd line treatment and post-progression off 2nd line treatment as the company enabled 2nd line treatments to be given beyond progression (i.e. the PFS and ToT curves can cross). Following treatment cessation or progression, patients can receive a subsequent therapy, described in Section 4.2.10.4. Figure 7 presents the company model schematic.

Figure 7. Model schematic (reproduced from Figure 24 of the CS)
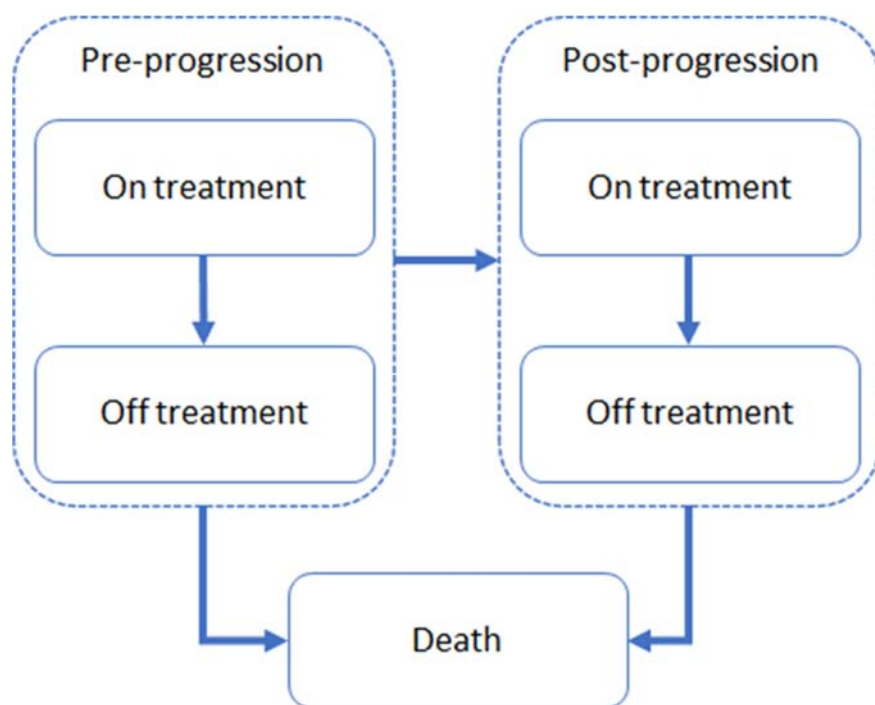
All patients enter the model in the progression-free health state and are assumed to be on NIVO+IPI or a comparator treatment. The proportion of patients occupying a health state during any given cycle is based on parametric survival curves for the clinical outcomes: PFS (used to model the pre-progression health state), OS and ToT (used to estimate the proportion of patients who are on 2nd line treatment). The proportion of patients occupying the post-progression health state for any given cycle is calculated as the difference between OS and PFS per cycle. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 4.2.2.

4.2.4.1 ERG critique

The ERG considers the company's model to capture all relevant health states. The ERG also notes that partitioned survival models have been accepted in a wide variety of oncology settings submitted for NICE appraisal.

However, as described in Section 3, the OS results from CheckMate 142 at the original data-cut (Feb 2019) and updated data-cut (Oct 2020) are very immature. Moreover, the heavy censoring present at the end of the KM curve (from month 46) may lead to implausible plateaus in the survival curve. As shown in Figure 69 of the CS, median PPS has been reached. As such, there is more KM to inform the extrapolation which should result in more reliable extrapolations. For these reasons, the ERG considers that an alternative model structure should have been considered by the company; that is,

a state transition model where PPS is explicitly modelled, and OS depends on the time spent in PFS and PPS. During the clarification stage, the company was asked to consider this alternative. In their response the company explained that survival data from CheckMate 142 is sufficiently mature to conclude that outcomes are significantly improved versus comparators. The company also highlighted that it would add uncertainty in terms of attempting to assign pre- and post-progression mortality, would require significant assumptions that may or may not be appropriate for different comparators (PPS outcomes are not available from the comparator studies) and would require a large amount of time to undertake.

Finally, the ERG's clinical experts disagreed with some of the transitions between the health states related to ToT. More information and critique of the methods used to estimate proportions of patients on treatment within each health state is provided in Section 4.2.6.1.2.

4.2.5   Perspective, time horizon and discounting

A weekly cycle length was implemented in the model and no half-cycle correction was applied. The time horizon in the model was set to 50 years (2,609 weeks). Based on a starting age of 56.6 years, patients would be 106.6 years old at the end of the time horizon. The perspective of the analysis is based on the UK National Health Service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.[60]

4.2.5.1   ERG critique

The ERG has no major issues with the omission of a half-cycle correction because the cycle length is short enough to allow robust estimates of costs and benefits to be calculated. The ERG also notes that the time horizon in the deterministic analysis could be shortened from 50 years to 45 years as this is the time all-cause mortality (ACM) caps OS to 0% survival. However, reducing the time horizon to 45 years has no impact on the deterministic cost-effectiveness results.

The ERG also notes that, if ACM is omitted from the model, 30% of patients remain alive in the NIVO+IPI arm at 50 years. This is related to the phenomenon that the probability of survival is higher for patients with the disease than the general population from year 32. Adjustments for ACM are discussed further in Section 4.2.6 and 4.2.7.

4.2.6   Treatment effectiveness

4.2.6.1   NIVO+IPI

Clinical data included in the model for NIVO+IPI is based on unadjusted individual patient level data from CheckMate 142 (Feb 2019 data cut) and includes IA (investigator assess) PFS, ToT and OS outcomes. To extrapolate the CheckMate 142 KM data, the company followed the guidelines for survival model selection outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14[55] and Bagust and Beale 2014[64].

Extrapolations of the KM data were then explored using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) and piecewise models (described as semi-parametric [SP] models in the CS). The company did not explore spline-based models in their submission because they considered them to be inappropriate when KM data is largely incomplete and lacking a statistical rationale for extrapolation. However, these were provided following a clarification request.

To select an appropriate distribution for the extrapolation of each outcome, the company assessed the fit of each modelled curve against the KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the fit over the observed period and consideration of the log cumulative hazard plots. The company also considered the clinical plausibility of the long-term hazard profile.

In Appendix M of the CS the company also noted that that PFS and OS may "plateau" for an extended period, with █████ hazard of death over the general population (██████████). As it is clinically infeasible that the marginal hazard would decrease indefinitely, the company decided that all models must be fitted in a "relative survival context", incorporating matched lifetable hazard of mortality (ACM) as a baseline hazard above which the parametric model (the extrapolation of CheckMate 142) would inform an additive disease-specific excess hazard. The following subsections focus on the disease-specific hazards from CheckMate 142. Adjustments for ACM are considered in more detail in Section 4.2.7.

During the clarification stage, PFS (IA and BICR) and OS outcomes from an updated data cut (Oct 2020) became available. However, PFS IA, ToT and OS extrapolations from the previous data cut (Feb 2019) were utilised in the economic analysis.

4.2.6.1.1 Progression-free survival (PFS)

The company highlighted that the KM plot for PFS showed a ███████████ hazard, with a ██ (Figure 2 in Section 3.3.1). ██. To substantiate this, the company produced Ishak diagnostic plots (Figure 31 in Appendix 9.11). Using these plots, the company stated that the ██████████████████ approaches a ██ and that none of the parametric models adequately reflected this █████████████████. The company also produced smoothed estimators of the hazard function (Figure 34 in Appendix 9.12) and noted that the ██, depending on which independent hazard smoother is considered. However, the company added that the earliest point at which a █████████████████ value could be considered would be near the point at which the estimators are at the value of the minimum value of the upper confidence bound of the bspline estimator (approximately 10 months for the bspline and kernel-smoothing estimators).

For these reasons, a semi-parametric (SP) model utilising KM data for the ████████████████████ was preferred. In the base case analysis, the company used KM data to month 6.44. According to the company, this represented a time beyond the initial period of regular imaging, where the PFS profile became ███, and treatment decisions were made less frequently, with implications of continuity for all considered outcomes. After this time point, the company's chosen curve was the exponential, which had the best fit statistics and a good visual fit. The company added that this was a conservative choice as the log-logistic provided a similarly close fit, with comparable long-term extrapolation and fits with hazard progression observed for immune-oncology therapies in other indications.

Parametric distributions fitted from month 6.44 are given in Figure 8. Figure 28 in Appendix 1.1 compares the modelled extrapolations from the Feb 2019 data cut with the KM data from the updated data cut (Oct 2020).

Figure 8. CheckMate 142 NIVO+IPI IA PFS SP extrapolation using a 6.44 month KM cut-off (reproduced from Figure 26 of the CS and Figure 8 of Appendix M)
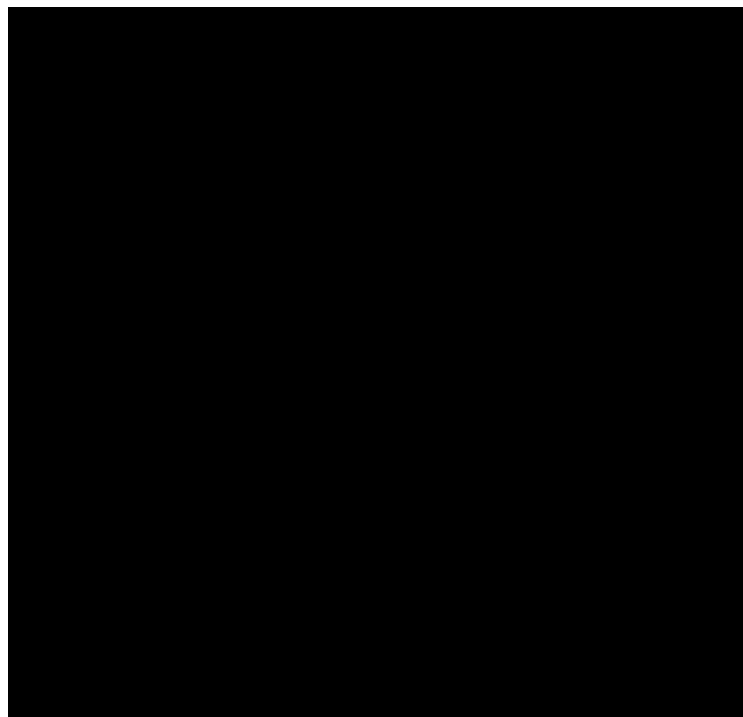
4.2.6.1.2 Overall survival (OS)

The company noted that the assumption of no excess hazard in the long term (i.e. a statistical cure) is uncertain. Therefore, the company preferred to maintain an excess hazard of death over the general population and use the same SP approach to model PFS and OS. This included the same KM data cut-off point (6.44 months). Parametric distributions fitted to OS data from month 6.44 are given in Figure 9. The exponential and Gompertz curves were both dismissed by the company, the exponential due to its constant hazard and the Gompertz due to its zero-excess hazard in the long-term. The company's chosen curve was the log-logistic. Figure 27 in Appendix 1.1 compares the modelled extrapolations from the Feb 2019 data cut with the KM data from the updated data cut (Oct 2020).

Figure 9. CheckMate 142 NIVO+IPI OS SP extrapolation using a 6.44 month KM cut-off (reproduced from Figure 27 of the CS and Figure 20 of Appendix M)
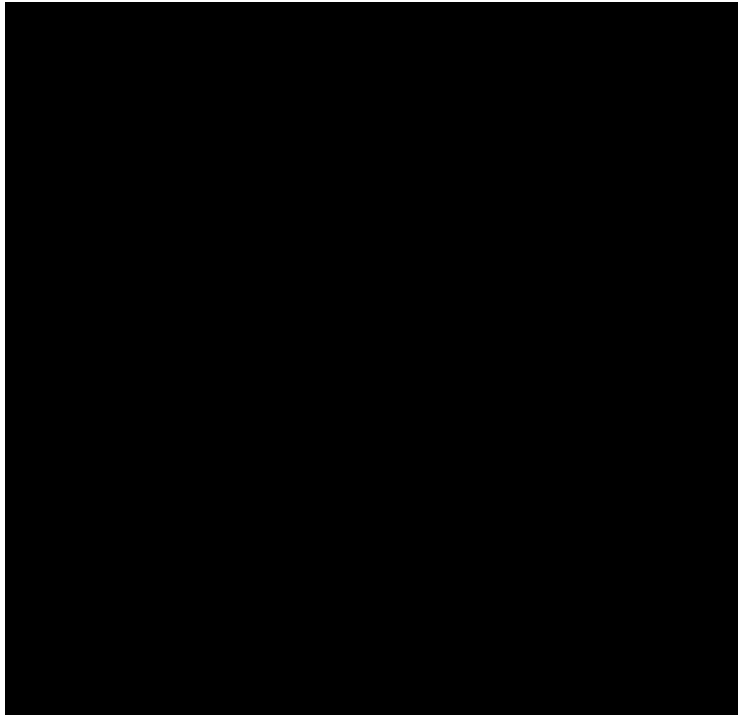
4.2.6.1.3 Time on treatment (ToT)

The model incorporates a ToT curve to inform the proportion of patients discontinuing treatment due to progression and AEs. For NIVO+IPI ToT was taken from CheckMate 142 and defined as time from treatment initiation to last dose for patients who have discontinued treatment was used to estimate the proportion. The model also includes a stopping rule: patients still receiving nivolumab treatment at two years are assumed to discontinue treatment.

Although no formal stopping rule was applied for nivolumab during CheckMate 142, the company considered this to be appropriate given that evidence in support of a two-year stopping rule is currently being collected from CheckMate 8HW[38] and CheckMate 142. More details on the protocol amendment to CheckMate 142 can be found in Section 2.3.2. The ERG also notes that the estimated primary completion date for CheckMate 8HW is not until August 2025.[38] However, preliminary results are expected in ███████.

The company also highlighted that a stopping rule at two years is frequently applied for nivolumab in other indications and, according to the company's clinical experts, it is considered standard clinical

practice in the treatment of mCRC. For these reasons, the stopping rule was included in the company's base case analysis. The company also provided a scenario analysis where no stopping rule is applied. As shown in Section 5.1.2.6, removing the 2-year stopping rule increases the ICER for NIVO+IPI above £30,000 per QALY in each comparison.

As for the ToT curve, the company considered a SP approach to be most appropriate, where KM data was applied until 6.44 months followed by a parametric extrapolation using the log-logistic distribution. The company noted that while the exponential distribution also provided an adequate fit, the log-logistic distribution provided less deviation from the KM data at 24 months (i.e. the point the stopping rule kicks in), and also provided a long tail, representative of continued treatment post-progression. Parametric distributions fitted from month 6.44 are given in Figure 10.

Figure 10. CheckMate 142 NIVO+IPI ToT SP extrapolation using a 6.44 month KM cut-off (reproduced from Figure 29 of the CS and Figure 31 of Appendix M)
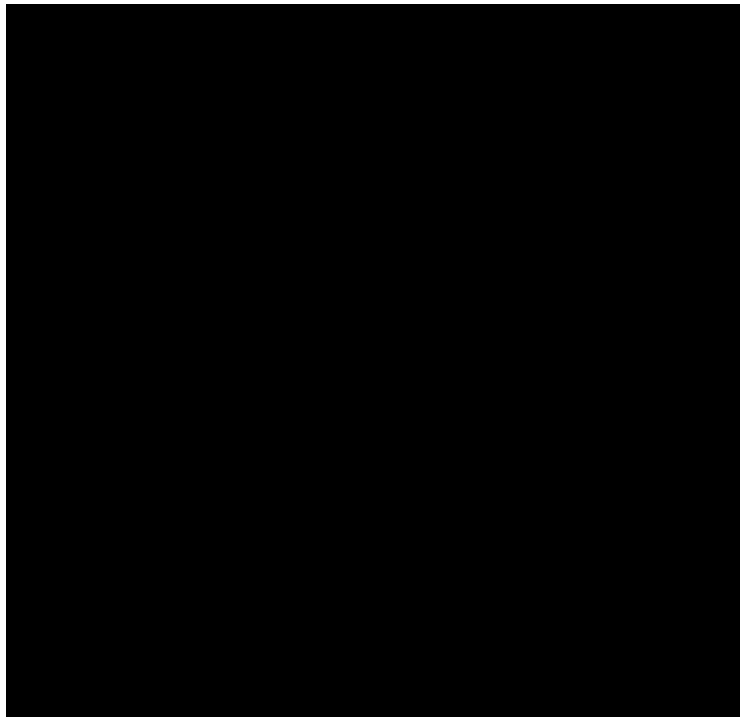
4.2.6.1.4   ERG critique

The ERG agrees with the company that the updated data cut provides observed data to ▮▮▮▮▮▮▮ and supports the continued benefit of NIVO+IPI, above the model predictions. However, there is heavy censoring present at the end of the KM curves from 46 months onward and data beyond this point are highly uncertain (see Figure 24 and Figure 25 in Appendix 1.1). Furthermore, only aggregate data are available from the latest data cut and therefore these data cannot be used to inform the matching-adjusted indirect comparisons (MAICs), which relies on the availability of individual patient data (IPD).

The ERG also agrees with the company that there is a ▮▮▮▮▮▮▮▮▮▮ hazard profile for PFS and ToT and that this ▮▮▮▮▮▮▮▮▮▮ is inadequately captured using a fully parametric model. However, the KM cut-off point chosen by the company to represent this change is debatable. The ERG also questions if spline-based models would be more suitable to model the ▮▮▮▮▮ hazard profiles. For OS, the ERG questions if a semi-parametric model is suitable at all due to the subtlety of the ▮▮▮▮▮▮▮▮▮▮▮ and the small number of events in the tail of the OS curve left to inform the extrapolation. These other types of models (spline-based models and fully parametric models) are discussed in greater detail in the Appendix.

Other issues include the relationship between the selected survival extrapolation in the model and the MAIC survival input, and some of the transitions between the health states related to ToT. Each of these issues is described in turn below.

Alternative survival curves

For PFS, the company's choice of KM cut-off is debatable. On the one hand, the company's KM cut-off point could be considered too late. Based on feedback from the ERG's clinical experts and looking at the KM curve (Figure 2 in Section 3.3.1) and cumulative hazard plot (Figure 11) the effect of the immunotherapies appears to start at around ███████████████████████████████.

Figure 11. Cumulative hazard plot with NIVO+IPI IA PFS and ToT from CheckMate 142 (reproduced from Figure 28 of Appendix M)
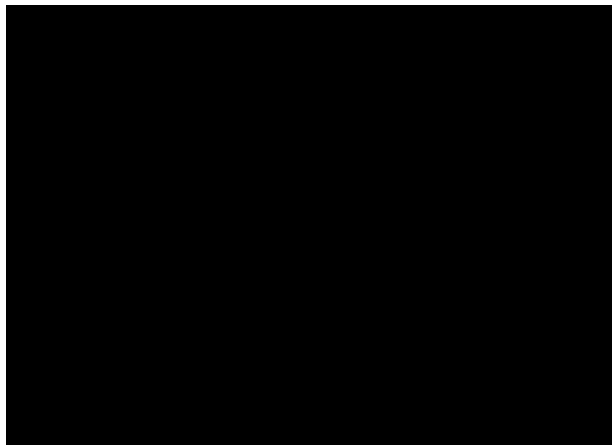
On the other hand, the company's cut-off point could be considered too soon. As noted by the company, the smoothed estimators of the hazard function (Figure 34 in Appendix 9.12), do not show a ████████████████ value until month 10. However, the ERG would recommend against a later cut as this would substantially reduce the amount of data that can be used to inform the long-term extrapolation.

For ToT, the ERG considers that the ████████████████████ approaches a ██ based on the cumulative hazard plot (Figure 11) and Ishak diagnostic plots (Figure 32 in Appendix 9.11) (around exp(1) on the Ln(Time) axis). Additionally, according to the smoothed hazard function estimates, the ToT hazard is at its ██

▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ (Figure 35 in Appendix 9.12). For these reasons, the ERG considers that using 6.44 months of KM data to inform the SP extrapolation unnecessarily reduces the amount of data that can be used to inform the long-term extrapolation for ToT.

For OS, the ERG finds it contradictory for the company to use the same SP approach to model PFS and OS when it is stated in the CS that "OS described a ▮▮▮▮▮▮▮▮ hazard profile than PFS" and "was represented by a ▮▮▮▮▮▮▮▮▮▮▮ hazard". The cumulative hazard plot in Figure 12 illustrates the company's statements well.

Figure 12. Cumulative hazard plot with NIVO+IPI IA PFS and OS from CheckMate 142 (reproduced from Figure 17 of Appendix M)
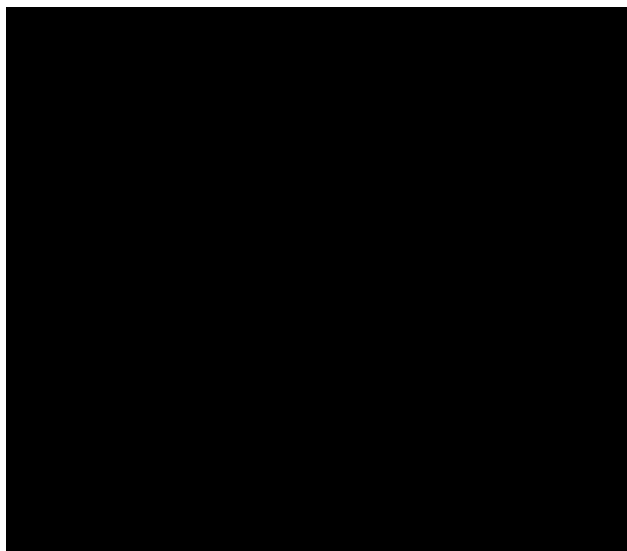
During the clarification stage, the company was asked to substantiate the use of a 6.44 months KM cut-off point for OS. In their response, the company stated that many KM cut-off points were explored and that some consideration to the PFS and ToT models was given. However, the company was unable to use the findings from the Ishak plots and smoothed hazard estimators to justify their cut-off point for OS.

As shown in Figure 33 in Appendix 9.11, the OS KM data track the regressions in the Ishak plots well from ▮▮▮▮▮▮▮▮▮▮▮ on the Ln(Time) axis). Additionally, the ERG's clinical experts expected the benefits of NIVO+IPI to become clinically meaningful after 3 months of treatment. Therefore, the ERG considers that using 6.44 months of KM data to inform the SP extrapolation

unnecessarily reduces the amount of data that can be used to inform the long-term extrapolation for OS.

Figure 14) and OS (Figure 15). As per the base case analysis, the company chose the exponential distribution as the best fitting distribution to inform the PFS extrapolation and the log-logistic distribution as the best fitting distribution to inform the ToT and OS extrapolations. During the factual accuracy check, the company identified an error in the economic model provided in response to this clarification question (CQ B5). This related to the implementation of ACM. All results in this report include the company's corrections provided during the factual accuracy check.

Figure 13. NIVO+IPI PFS extrapolation using data cut at 2.99 months (reproduced form Figure 41 of the company's clarification responses)
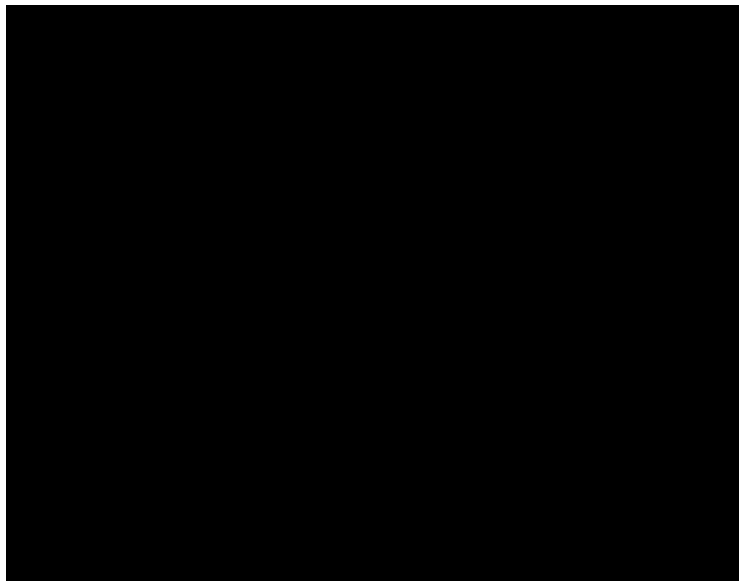
Figure 14. NIVO+IPI ToT extrapolation using data cut at 2.99 months (reproduced form Figure 40 of the company's clarification responses)

Figure 15. NIVO+IPI OS extrapolation using data cut at 2.99 months (reproduced form Figure 42 of the company's clarification responses)
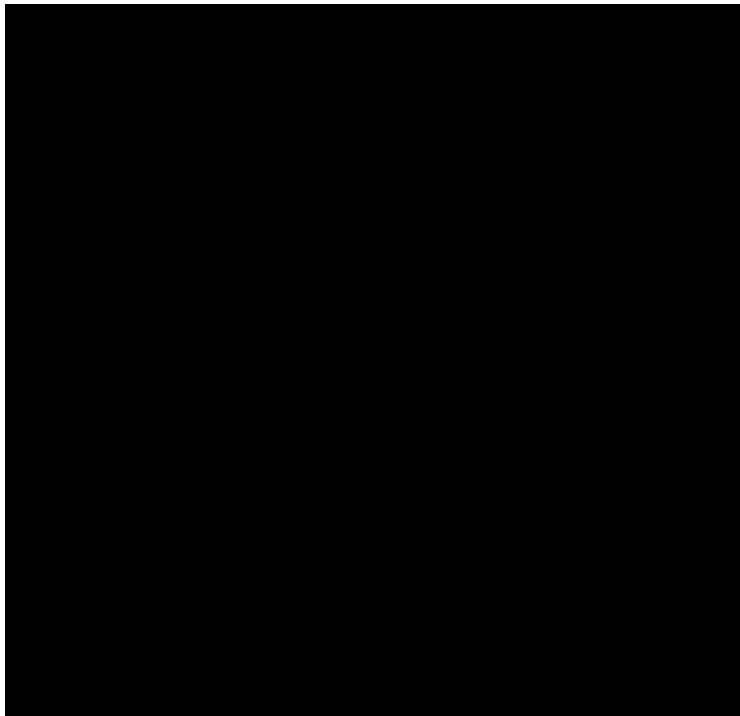
Compared to the base case analysis, a 2.99-month KM cut-off reduced the mean and median PFS time (including ACM) from ███████████████████████ to ███████████████████,

respectively. For OS, the mean and median OS time increased (including ACM) from

████████████████████████████ to ███████████████████████, respectively.

However, these results were not fully utilised in the economic analysis provided to the ERG. This is because the model was only set up to include MAIC output (relative mean survival estimates) based on the base case extrapolation for NIVO+IPI (KM to 6.44 months followed by an exponential extrapolation for PFS and a log logistic extrapolation for ToT and OS). To address this issue, the ERG requested the company to link the selection of NIVO+IPI extrapolations in the economic analysis with MAIC survival inputs. Following another round of clarification, the company provided the MAIC output needed to inform the model using the aforementioned semi-parametric models with a 2.99-month KM cut-off. These MAIC outputs are summarised by the ERG in Section 3.4.4.

Cost-effectiveness results using alternative survival curves

Figure 16 and Figure 17 illustrate the company's base case curves for PFS and OS alongside the curves considered by the ERG, with and without ACM adjustments.

As mentioned earlier, the ERG considers the semi-parametric models, with KM data up to 2.99 months, the most appropriate for PFS, ToT and OS and will employ these models in its base case analyses (see Section 6). The key reason for choosing these models is because they represent the ████████████ hazard well and extend the amount of data that can be used to inform the long-term extrapolation. The spline-based model for PFS and the fully parametric model for OS (described in detail in the Appendix) could also be disregarded due to their poorer fit statistics.

The ERG also sought clinical expert advice on the plausibility of these curves. They advised the ERG that long-term projections are impossible to predict and that all curves are clinically plausible. The ERG also notes that a considerably longer follow-up period would be necessary (potentially 10 years or above) to validate the curves generated from CheckMate 142.

Figure 16. Key NIVO+IPI PFS extrapolations, generated by the ERG
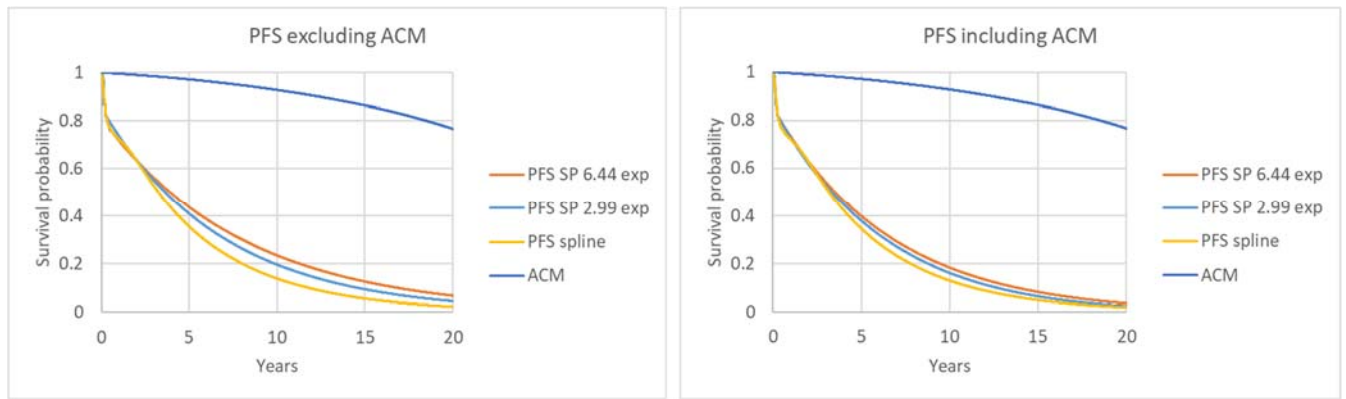
Figure 17. Key NIVO+IPI OS extrapolations, generated by the ERG
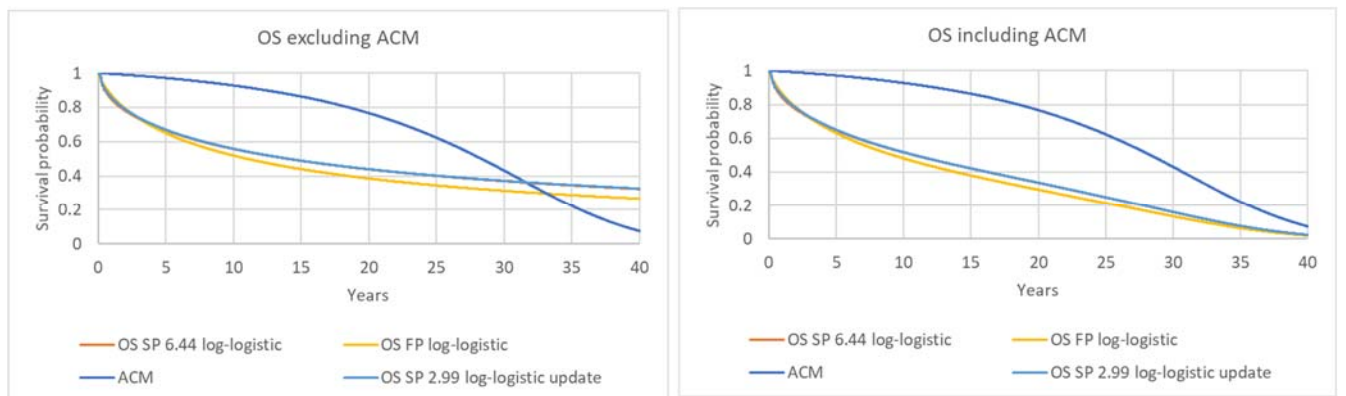
During the final round of clarification, the company provided cost-effectiveness results using different combinations of these curves. These results include the link between the survival extrapolation in the economic analysis and the MAIC survival input. As shown in Table 27, the cost-effectiveness results are quite robust to alternative survival extrapolations.

Table 27. Cost-effectiveness results using alternative PFS and OS curves proposed by the ERG

| Comparator | Source | ICER (£/QALY) | |
		MAIC (partially adjusted)	Unadjusted analysis (naïve comparison)
PFS: SP model, KM to 2.99 months followed by an exponential distribution OS: SP model, KM to 2.99 months followed by a log logistic distribution ToT: SP model, KM to 2.99 months followed by a log logistic distribution			
TRI-TIP	RECOURSE EUR	£13,388	£13,247
BSC	RECOURSE EUR	£14,187	£14,118

FOLFOX	CONFIRM2	£15,194	£15,029
FOLFIRI	RAISE	£15,410	£14,988
	VELOUR	£16,481	£14,944

PFS: spline-based model

OS: SP model, KM to 2.99 months followed by a log logistic distribution

ToT: SP model, KM to 2.99 months followed by a log logistic distribution

TRI-TIP	RECOURSE EUR	£13,693	£13,471
BSC	RECOURSE EUR	£14,444	£14,335
FOLFOX	CONFIRM2	£15,327	£15,267
FOLFIRI	RAISE	£15,741	£15,224
	VELOUR	£16,712	£15,179

PFS: SP model, KM to 2.99 months followed by an exponential distribution

OS: FP model, log logistic distribution

ToT: SP model, KM to 2.99 months followed by a log logistic distribution

TRI-TIP	RECOURSE EUR	£14,005	£13,843
BSC	RECOURSE EUR	£14,844	£14,747
FOLFOX	CONFIRM2	£16,089	£15,785
FOLFIRI	RAISE	£16,269	£15,734
	VELOUR	£17,147	£15,684

PFS: spline-based model

OS: FP model, log logistic distribution

ToT: SP model, KM to 2.99 months followed by a log logistic distribution

TRI-TIP	RECOURSE EUR	£14,330	£14,079
BSC	RECOURSE EUR	£15,118	£14,976
FOLFOX	CONFIRM2	£16,231	£16,039
FOLFIRI	RAISE	£16,625	£15,985

	VELOUR	£17,390	£15,934

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; KM, Kaplan Meier; LYs, life years; QALYs, quality-adjusted life years; SP, semi-parametric; ToT, time on treatment; TRI-TIP, trifluridine-tipiracil

Stopping rule

Clinical experts advising the ERG noted that the company's modelling of ToT does not reflect how nivolumab is used in clinical practice. The ERG's clinical experts fed back that their preference would be to continue nivolumab treatment until disease progression and not to take patients off nivolumab treatment if they are still deriving a benefit and remain progression-free at 2 years. Additionally, patients would only rarely be treated beyond progression if they are considered to have a pseudo progression, where a confirmatory scan would be required, or if they are progressing very slowly but still considered to deriving substantial clinical benefit. In either case, treatment beyond progression would be unlikely to occur for more than a few months. To address clinical expert concerns, the company was asked to provide a scenario analysis where the treatment stopping rule is removed and nivolumab cannot continue beyond progression. In their response, the company explained that immunotherapies can lead to enlarged tumours and these may be interpreted as progressions even though they are associated with positive clinical outcomes (pseudo progressions). The company also provided the requested scenario. This led to ICERs for NIVO+IPI between £22,000 and £24,000, depending on the comparator chosen.

During the clarification stage, the company also confirmed that ▮ patients continued to receive nivolumab post progression during CheckMate 142. As such, the ERG considers it necessary to allow treatment beyond progression in order to reflect the cost of treatment received in CheckMate 142 and therefore, match the effectiveness data used in the analysis. Likewise, the ERG considers that the 2-year stopping rule should be removed from the economic analysis as no formal stopping rule was applied during CheckMate 142 or is expected to be in the marketing authorisation. The ERG also notes that the committee for TA439[66] concluded that it was inappropriate to implement a stopping rule in people with mCRC.

4.2.6.2 Comparators

In the base case analyses, clinical data for the comparators is based on the MAIC mean survival estimates for PFS and OS. This MAIC is described in detail in Section 3.4. In brief, the MAIC

represents comparator data "partially adjusted" to the population in CheckMate 142. A summary of the MAIC methods and results is given in Table 28 for PFS and Table 29 for OS.

To estimate a survival curve for each comparator, the company fitted an exponential distribution to produce an area under the curve that is equal to the MAIC mean survival estimate (the last column in Table 28 and Table 29). The company referred to the advice in Bagust and Beale 2014[64] that the default parametric distribution is an exponential distribution when there is no available evidence to inform the hazard profile.

In scenario analyses the company considers unadjusted comparator data (a naïve comparison) and pooled comparator data as alternatives to the MAIC. These alternative methods and results are discussed in greater detail in Section 3.4 and 5.1.2.3, respectively.

Table 28. Summary of PFS MAIC comparator data

Study	Scenario: key reason	PFS distribution applied to digitised data	Unadjusted mean PFS, months	Adjusted mean PFS, months
FOLFOX				
CONFIRM2	Base case: large scale RCT; relevant patient pathway; patient characteristics similar to CM142	Lognormal	5.47	4.49
FOLFIRI				
RAISE	Scenario: large study, representative median outcomes, treatment history required bevacizumab plus FOLFOX, which is not relevant to UK treatment pathway	Lognormal	6.62	7.54
VELOUR	Base case: large study, representative median outcomes, treatment history similar to CM142	Lognormal	6.79	6.33
TRI-TIP				
RECOURSE/ EUR	Base case: large study; reflects CM142 and comparator studies	Generalised gamma	3.68	4.19

RECOURSE/USA	Scenario: 21 study sites in the USA'	Generalised gamma	3.63	3.70
BSC				
RECOURSE/EUR	Base case: large study; reflects CM142 and comparator studies	Log-logistic	1.83	2.10
RECOURSE/USA	Scenario: 21 study sites in the USA'	Log-logistic	1.87	1.90
Abbreviations: CM142, CheckMate 142; FOLFIRI, 5-FU folinic acid and irinotecan; FOLFOX, 5-FU folinic acid and oxaliplatin; TRI-TIP, trifluridine-tipiracil; RCT, randomised controlled trial; ToT, time on treatment				

Table 29. Summary of OS MAIC comparator data

Study	Scenario: key reason	OS distribution applied to digitised data	Unadjusted mean OS, months	Adjusted mean OS, months
FOLFOX				
CONFIRM2	Base case: large scale RCT; relevant patient pathway; patient characteristics similar to CM142	Lognormal	17.32	15.65
FOLFIRI				
RAISE	Scenario: large study, representative median outcomes, treatment history required bevacizumab plus FOLFOX, which is not relevant to UK treatment pathway	Generalised gamma	16.23	17.19
VELOUR	Base case: large study, representative median outcomes, treatment history similar to CM142	Generalised gamma	15.70	15.30
TRI-TIP				
RECOURSE/EUR	Base case: large study; reflects CM142 and comparator studies	Lognormal	10.39	10.86

RECOURSE /USA	Scenario: 30 study sites in China, the Republic of Korea and Thailand	Lognormal	11.71	11.70
BSC				
RECOURSE /EUR	Base case: large study; reflects CM142 and comparator studies	Generalised gamma	7.22	7.55
RECOURSE /USA	Scenario: Japanese	Generalised gamma	8.07	8.13

Abbreviations: CM142, CheckMate 142; FOLFIRI, 5-FU folinic acid and irinotecan; FOLFOX, 5-FU folinic acid and oxaliplatin; TRI-TIP, trifluridine-tipiracil; ToT, time on treatment

Comparator ToT is based on the base case MAIC evidence sources but is applied without any adjustments for effect modifiers or prognostic variables. No KM data for ToT or time to discontinuation was identified in these sources. As such, mean and median data was extracted and standardised as far as possible. The ToT data used to estimate a curve based on an exponential distribution is given in Table 30. Patients do not discontinue BSC in the economic analysis.

Table 30. Comparator ToT data used in the economic analysis

Treatment	ToT	Exponential λ, months	Source
FOLFIRI	Median: 4.2 months, 18.1 weeks*	0.167	VELOUR[44]
FOLFOX	Median: 4.3 months, 18.7 weeks*	0.161	CONFIRM 2[47]
TRI-TIP	Mean: 2.9 months, 12.7 weeks**	0.344	RECOURSE[67]

Abbreviations: FOLFIRI, 5-FU folinic acid and irinotecan; FOLFOX, 5-FU folinic acid and oxaliplatin; TRI-TIP, trifluridine-tipiracil; ToT, time on treatment

*Median values converted to exponential rates using formula: rate = ln(2)/median

**Mean values converted to exponential rates using formula: rate = 1/mean

4.2.6.2.1   ERG critique

The ERG was surprised the company chose an exponential distribution to model comparator mean survival when other distributions were chosen to model the digitised unadjusted comparator data. The ERG acknowledges there are no hazard profiles on the adjusted comparator data, but it would not be unreasonable to assume they are the same. In response to a clarification request, the

company provided results using the same parametric distributions used to estimate survival in the MAIC. However, using these longer-tailed distributions decreased the ICER by less than £100 in most cases.

As noted in Section 3.4.3, the ERG considers BRAF/KRAS status to be an important prognostic factor. In response to a clarification request the company attempted to address the poor reporting of KRAS/BRAF for relevant comparators and place greater weight on studies reporting patient characteristics for important prognostic factors such as BRAF/KRAS status. Despite changing comparator studies and adjusting for additional covariates, the cost-effectiveness outcomes were similar (see Table 60). However, the ERG notes that the company is still not adjusting for all important covariates in this analysis.

According to NICE DSU TSD 18[68], all effect modifiers and prognostic variables should be adjusted for in an unanchored comparison. During the clarification stage, the company provided MAIC results from an "all available" adjustment set (see Section 3.4.4). However, the company refused to provide cost-effectiveness results as the company considered these comparator outcomes to lack face validity due to low effective sample size (ESS). As explained in Section 3.4.4 and Section 3.5, the ERG appreciates that these results are likely to be highly uncertain, but the ERG would prefer more accurate albeit more uncertain results. Additionally, given that the comparator mean survival outcomes are generally improved when all available covariates are adjusted for, the ERG considers that the results would reduce the decision risk for approving NIV+IPI if they fall below the NICE threshold for cost-effectiveness. For completeness, the ERG has generated results using the data provided by the company for the "all available" adjustment set. These results can be found in Section 6.3. Briefly, the ICER increases for NIVO+IPI in each comparison yet remains below the standard NICE lower threshold of £20,000 per QALY.

Based on these results, the ERG considers it reasonable to assume that there is a benefit in PFS and OS for NIVO+IPI over each comparator but that the magnitude of the benefit is highly uncertain. Additionally, in the absence of a valid fully adjusted MAIC, the ERG considers the use of an unadjusted comparison (naïve comparison) to be the least biased approach to compare NIVO+IPI and the comparators as it is transparent in terms of the likely biases that exist within the comparison and the analysis itself has not introduced additional bias into the comparison. The limitations associated with each MAIC are given in detail in Section 3.4.4 and Section 3.5.

Furthermore, the ERG is unclear why the company did not adjust ToT using an MAIC, as per PFS and OS. This is important because there is a disconnect between PFS and ToT if only one of these outcomes is adjusted. As such, the ERG considers this to be another reason to prefer the unadjusted comparison (naïve comparison).

Additionally, the ERG notes that there is another disconnect regarding the mean PFS and OS estimates between the economic analysis and MAIC. These are summarised in Table 31. In response to a clarification request on this, the company stated that, "*MAIC outcomes… do not reflect the impact of ACM, which is applied as an additional source of mortality in the model. Hence the modelled OS outcomes vary slightly from the MAIC outcomes*". This is contradictory to another response from the company on ACM, "*For the comparator, the means informing the relative mean value from the ITC are both inclusive of general population ACM…In order to prevent the model applying ACM to the modelled comparator survival curve, the mechanism to prevent double-counting in the piecewise models is used, setting ACM multiplication to start at the final model cycle*". Moreover, if the MAIC estimates do not reflect the impact of ACM, the estimates from the MAIC should be higher than the estimates from the economic analysis, not lower. In consequence, the ERG is of the opinion that all estimates in Table 31 are undiscounted and include ACM and suspects the differences are a result of the company calculating MAIC means outside the economic model. Also, as the economic analysis inflates NIVO+IPI and comparators mean estimates by a similar magnitude, the ERG is satisfied no major bias has been introduced into the analyses.

Table 31. Mean PFS and OS estimates in the economic analysis vs MAIC (company base case)

Treatment (study)	Mean PFS, months		Mean OS, months	
	Economic analysis	MAIC	Economic analysis	MAIC
NIVO+IPI (CheckMate 142)	■■	■■	■■	■■
TRI-TIP (RECOURSE EUR)	4.31	4.19	10.98	10.86
BSC (RECOURSE EUR)	2.22	2.10	7.67	7.55
FOLFOX (CONFIRM2)	4.61	4.49	15.77	15.65
FOLFIRI (RAISE)	6.44	6.33	15.41	15.30

Except for FOLFIRI, the ERG is generally in agreement with the base-case evidence source chosen for each comparator. During the clarification stage the company explained VELOUR was chosen as the base-case evidence source for FOLFIRI because RAISE required treatment with a specific first-line regimen (bevacizumab plus FOLFOX), which is not included in the UK treatment pathway. The ERG's clinical experts advised that prior bevacizumab may have an effect on prognosis but is unlikely to affect the efficacy of NIVO+IPI. The ERG also notes that there are issues with VELOUR as not all patients in the trial were pre-treated in the advanced setting. For these reasons, the ERG considers RAISE and VELOUR to be equally relevant. More details on the ERG's assessment of each comparator trial can be found in Section 3.4.1. Nonetheless, as shown in Section 5 and Section 6, changing the base-case evidence source has a minimal impact on the cost-effectiveness results.

Finally, in response to a clarification question on the ToT calculations, the company expressed a preference for using means over medians, when reported. However, to inform ToT for FOLFOX, the company employed a median of 4.3 months when a mean of 5.1 months is also reported[47]. The ERG has explored the impact of using this mean ToT estimate for FOLFOX in scenario analysis (see Section 6.2).

4.2.7   Mortality

Disease-specific mortality and ACM is accounted for in KM data. In the company's base case analyses, PFS and OS for NIVO+IPI is based on 6.44 months of KM data followed by a parametric survival distribution. For this reason, the company only accounted for increasing ACM from 6.44 months (29 weeks). Using UK life tables[53], the company created a survival curve to represent ACM. Then, the two survival functions (PFS and ACM, and OS and ACM) are combined multiplicatively. This is illustrated in Figure 18.

Figure 18. NIVO+IPI (N/I) survival curves with and without ACM (generated by the ERG)
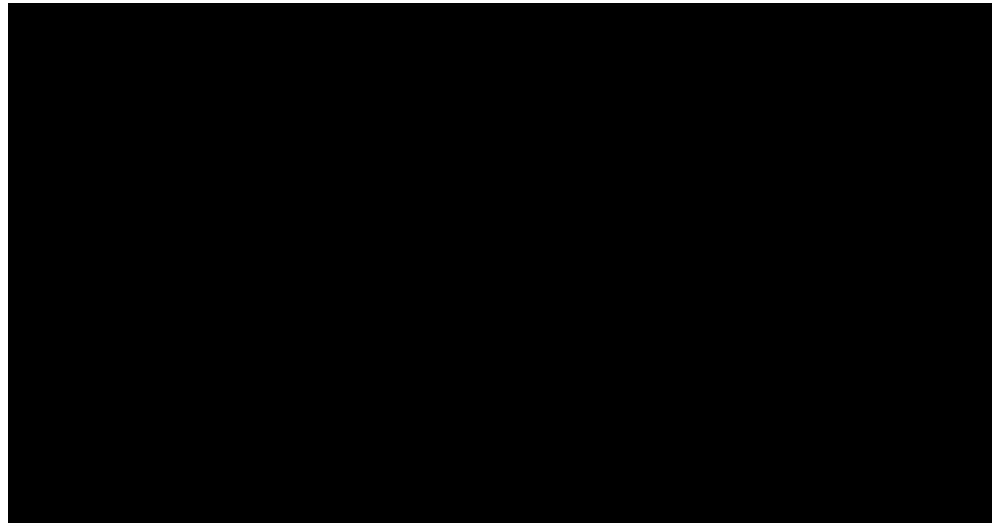
For the comparators, the means informing the relative mean value from the MAIC are both inclusive of ACM. This relative mean is then multiplied by a reference mean from a model of the CheckMate 142 NIVO+IPI population including ACM, therefore the adjusted mean is inclusive of both components. As such, ACM is not applied to the comparator survival curves in the model.

ERG critique

Based on TSD 21[65], the ERG considers that the company should be using an excess mortality model where they disaggregate the "excess risk" from the disease from ACM and then apply both, with the view that in the long term the hazard of death from the condition might decrease whereas ACM would increase. In response to a clarification question on how the approach in the CS aligns with the advice in TSD 21, the company made no reference to TSD 21. The ERG is unable to suggest what impact an excess mortality model would have on the results. It is possible that the results from this alternative analysis will be consistent with those reflected in the CS.

The ERG also notes that the company made no ACM adjustments to ToT. The ERG considers this to be a reasonable omission as no treatment is given beyond 2 years in the company's base case analyses. However, when the treatment stopping rule for nivolumab is removed, the ERG considers this adjustment necessary to align PFS and ToT. Results of the ERG's analyses including an ACM adjustment for ToT are given in Section 6.

4.2.8 Adverse events

For NIVO+IPI, the company considered grade 3 or higher treatment-related adverse events (TRAEs) that were reported by at least two patients in the CheckMate 142 trial to include in the model. The company then excluded the two most common TRAEs because of their low-cost profile: ██████████████████████████████████████. The company also excluded seven other TRAEs because of their low incidence and low-cost profile: ██ ████████████████████████████. A table of the TRAEs considered by the company is given in Table 30 of the CS. Table 32 summarises the TRAEs included in the model.

The incidence of comparator TRAEs is based on published evidence (MAIC evidence sources). The rates of TRAEs applied in the model are summarised in Table 32 for each treatment. The company noted that TRAE causality was not reported in the VELOUR and CONFIRM 2, however, rates are presented and it is assumed that they are caused by the associated drug treatments. The company also assumed unreported TRAEs were not applicable and equal to zero.

The impact of TRAEs on patients' quality of life (QoL) is discussed in Section 4.2.7. The cost of managing each TRAE is discussed in Section 4.2.8.

Table 32. TRAE rates applied in the model (adapted from Table 31 of the CS)

	NIVO+IPI	BSC	FOLFIRI	FOLFOX	TRI-TIP
Source	CheckMate 142	RECOURSE[67]	VELOUR[44]	CONFIRM 2[47]	RECOURSE[67]
N	119	265	605	420	533
Colitis	██	NR	NR	NR	NR
Diarrhoea	██	0	7.80%	8.33%	2.25%
Anaemia	██	1.89%	4.30%	NR	12.20%
Fatigue	██	1.89%	NR	7.38%	2.06%
Hepatitis	██	NR	NR	NR	NR
Rash	██	NR	NR	NR	NR
Thrombocytopenia	██	0.38%	1.60%	4.05%	1.69%
Acute kidney injury	██	NR	NR	NR	NR

| Dyspnoea | ■■■ | NR | NR | NR | NR |
| Hypophysitis | ■■■ | NR | NR | NR | NR |

ERG critique

The ERG's clinical experts confirmed that the TRAEs chosen by the company are the most important TRAEs to consider as they are generally associated with the largest cost and quality of life implications. The ERG's clinical experts also added that patients on NIVO+IPI may require additional monitoring for immune-related AEs. Monitoring costs are discussed further in Section 4.2.10. The ERG also notes that the company's decision to assume comparator unreported TRAEs are equal to zero is conservative.

4.2.9   Health-related quality of life

In CheckMate 142, HRQoL data was recorded at baseline then at six weekly intervals until the end of treatment. Following discontinuation of treatment patients were assessed two more times after treatment. The company also describes recording HRQoL 'sporadically' during survival follow up. Measurement of HRQoL was based on the EQ-5D-3L instrument and valued using UK preference scores from Dolan 1997[69].

The company split utility values in the NIVO+IPI arm by treatment status (on-treatment and off-treatment). For the comparators, the company used utility values according to progression status (pre-progression and post-progression).

For the on-treatment utility value, the company used CheckMate 142 data. The on-treatment utility value includes measurements from progression-free patients on-treatment and patients who had clinically progressed but remained in receipt of treatment because the clinician believed there was a clinical benefit to continuing treatment. In Appendix N of the CS, the company provided utilities over various periods in the on-treatment dataset (Table 33).

The company chose the mean utility in the on-treatment dataset, inclusive of baseline, to inform the model. In the CS, the company concluded that the utility value from the chosen dataset (■■■■) was comparable to the population norm (0.842)[70] and broadly equivalent to utility values observed from

other NIVO+IPI indications, indicating that this utility gain may be due to the novel mechanism of action. These comparisons are summarised by the company in Table 33 of the CS.

Table 33. Mean Dolan TTO utilities over various periods in the on-treatment dataset (reproduced from Table 7 of Appendix N)

Dataset	MSI-H Nivolumab + Ipilimumab, mean [SE] (95% CI)
Baseline	███████████
Week 7	███████████
Baseline + on treatment	███████████
On-treatment (excluding baseline)	███████████
On-treatment week 13+	███████████

Abbreviations: CI, confidence interval; MSI-H, microsatellite instability high; TTO, time trade-off; SE, standard error.

For the comparators, the company applied utility according to progression status and used the pre-progression and post-progression utility values recorded in the CORRECT trial[1]. The post-progression utility value in the CORRECT trial was also used to inform the off-treatment utility value in the NIVO+IPI arm as data in CheckMate 142 were limited for patients who had discontinued treatment or experienced a progression event.

The company considered the utility values from the CORRECT trial to be reflective of standard care in a relevant mCRC population. The CORRECT trial was a second line drug trial in patients with mCRC and HRQoL was measured using the EQ-5D-3L instrument. The ERG notes that these patients did not have MSI-H/dMMR.

Table 34 summarises the utility data applied in the company's base case analyses. In scenario analyses, the company used the CORRECT utility values to inform the NIVO+IPI arm (NIVO+IPI utility values were assumed as per comparators and applied by progression status, as opposed to treatment status). As shown in Section 5.1.2.6, this scenario had a minimal impact on the ICER. This is because patients in the NIVO+IPI arm spend a shorter amount of time on the high on-treatment utility value (████) and a longer amount of time on the pre-progression utility value (0.75).

Table 34. Utility values applied in the model (reproduced from Table 34 of the CS)

Comparator	State	Utility value mean (SE)	Source
NIVO+IPI	On treatment	████████)	CheckMate 142
	Off treatment	0.69 (0.07)	CORRECT[1]
Comparators	Pre-progression	0.75 (0.08)	CORRECT[1]
	Post-progression	0.69 (0.07)	

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

The company also included age-related utility decrements in the model using a published algorithm by Ara and Brazier 2010[70]. The company did not include disutilities due to AEs as they were assumed to be captured within the regular HRQoL assessments.

ERG critique

The ERG considered whether the utility values derived from CORRECT[1] are representative of people with MSI-H/dMMR, who may have a lower QoL than the broader population with mCRC. However, the ERG's clinical experts advised that they would expect QoL to be similar in a patient with and without dMMR/MSI-H. In other words, QoL is related to progression status and not molecular abnormality. Thus, CORRECT could be an appropriate source to inform HSUVs by progression status in a dMMR/MSI-H mCRC population.

Following a clarification request, the company compared the baseline characteristics in CORRECT with the baseline characteristics in CheckMate 142 (see Table 53 in the company's response to CQ B17). Age and sex are comparable between the two studies, but the proportion of Asian patients is slightly higher in CORRECT than CheckMate 142. The company also highlighted that patients in CORRECT had more experience with anti-VEGF treatment, and were more likely to have KRAS mutations. On the other hand, they were less likely to have ECOG status 1 and BRAF mutations. Although it is difficult to predict the impact of these different characteristics on HRQoL, the ERG is cautious about combining utility values from CheckMate 142 and CORRECT in the same analysis and would prefer one source for consistency.

The ERG also sought clinical expert advice on how the company's on-treatment utility value for NIVO+IPI compares with other treatments and with patients without mCRC. The ERG's clinical experts made three key points:

- they would not expect a meaningful difference in the HSUVs between treatments and concluded that a novel mechanism of action alone was insufficient to warrant treatment-specific utility values;
- they would expect someone receiving second line treatment for mCRC to have a lower QoL than the general population (some patients may value their life very highly because they are thankful to be alive, but this would be overridden with the consequences of mCRC); and,
- they would expect the toxicities associated with IPI to have a large negative impact on patients' QoL.

The ERG notes that the company appears to agree with the clinical experts' point on general population mortality in Appendix N. Additionally, the points made by the company in Appendix N on general population mortality conflict those in the CS. In Appendix N, the company states that, "*For face validity, the on-treatment utility within cost-utility analysis will be assumed to not exceed a matched population norm. As above, for an English cohort matched by age and sex to the analysed cohort from CheckMate 142, mean utility was expected to be ▓▓▓▓. Thus, all long-term models constructed using these data (Table 7) exceed this value.*" In the CS, the company states, "*this is comparable with general population utility value (0.842)*." Nonetheless, the ERG considers that the on-treatment utility value is likely to be too high.

During the clarification stage, the company was asked to split the on-treatment utility value by progression status. These values are given in Table 35. The ERG does not understand why the overall on-treatment value (▓▓▓▓) is ▓▓▓▓ than the PFS on-treatment value (▓▓▓▓) and PD on-treatment value (▓▓▓▓). The ERG also notes that the PD HSUV is associated with the ▓▓▓▓ utility which is clinically implausible. These findings would benefit from further explanation from the company. For completeness, the ERG has employed these values in scenario analysis (see Section 6.2).

Table 35. CheckMate 142 utility values received during the clarification stage (adapted from Table 54 of the company's clarification responses)

Health state	Observations	Utility (95% CI)
PFS	1759	0.839 (0.821,0.857)

PFS, on treatment	1651	0.837 (0.818,0.856)
PD	208	0.850 (0.804,0.896)
PD, on treatment	66	0.728 (0.603,0.852)
On treatment	▮	▮▮▮▮

*assumed based on ▮ baseline observations and ▮ on treatment observations reported in Appendix N of the CS

Abbreviations: CI, confidence interval; PD, progressed disease; PFS, profession free survival

Furthermore, the ERG cannot identify the HSUVs used by the company in the CORRECT publication.[1] The pre-progression HSUV is similar (0.75 vs 0.74), but there is a large discrepancy in the post-progression HSUV (0.59 vs 0.69). The values identified by the ERG in the publication were also used and accepted in TA405.[2] During the factually accuracy check, the company explained that the HSUVs were taken from TA242[71], not CORRECT, and that TA242 was noted as the HSUV source in Table 22 of the CS. However, the company acknowledged that CORRECT was used as the reference thereafter. TA242 was published in 2012 and includes the assessment of cetuximab, bevacizumab and panitumumab for the treatment of mCRC after first-line chemotherapy.

The ERG is concerned that the company has not justified why the HSUVs in TA242 were preferred to those in CORRECT and that the company did not pick up on this discrepancy when asked about the CORRECT population during the clarification stage. The ERG for TA242 also noted that the PD HSUV applied in the CS could be too high, "The value of 0.69 for all patients in PD is probably an overestimate because it is likely that many patients were alive for several months after their last HRQoL questionnaires, because of the limited data cut-off time". To substantiate this point, the ERG for TA242 also noted that, "… in the economic evaluation of bevacizumab for first-line treatment and cetuximab plus irinotecan for second-line and further treatment of mCRC, Tappenden and colleagues (2007) assumed a utility of 0.80 in PFS and 0.60 in PD, independent of treatment." Furthermore, CORRECT may better reflect clinical practice today, CORRECT was published by Grothey *et al.* in 2013, while the HSUV source in TA242 was published in 2007[72]. Cost-effectiveness results based on the HSUVs used in CORRECT and TA405 can be found in Section 6.

To address the clinical experts' final point on the disutility associated with IPI, the ERG's considers using the lower week 7 utility for NIVO+IPI (▮▮▮▮) for the first 7 weeks of treatment, to be a reasonable scenario analysis for the on-treatment utility (see Section 6.2).

Overall, in the absence of utility values observed in a randomised controlled trial with an appropriate comparator arm, the ERG cannot justify the use of utility values according to treatment status. As such, the ERG's preference is to use the CORRECT utility values according to progression status in its base case.

Due to time constraints the ERG has been unable to add the utility decrements associated with TRAEs to this analysis. The ERG does not agree with the company that it is not possible to model these due to the paucity of data. However, given that the TRAEs associated with IPI are short lived the ERG does not consider this to be a major issue.

4.2.10 Resource use and costs

The company included the following costs in the economic model: drug acquisition and administration costs, disease management costs (health state costs), adverse event costs, subsequent therapy costs and end of life costs. The company also considered MSI testing costs in scenario analyses. The ERG also notes that unit costs used were inflated to 2018/2019 prices using the PSSRU hospital and community health services pay and prices index.[59]

4.2.10.1 Medication costs (acquisition and administration)

The intervention considered for the economic analysis is NIVO+IPI, both are given as intravenous infusions. Nivolumab is a variable dose drug that is dosed based on body weight at 3mg per kilogram (kg). The company base case assumes a mean body weight of 73.7kg (based on data from CheckMate 142). For nivolumab this results in a dose of 240mg, which assumes wastage of the rest of the vial. In the first four treatment cycles ipilimumab is given alongside nivolumab. Ipilimumab is dosed at 1mg per kg of bodyweight. Based on a mean body weight of 73.7kg, the dose per treatment cycle for ipilimumab is assumed to be 100mg, which includes vial wastage. From treatment cycle five onwards, nivolumab is given as a monotherapy.

A patient access scheme (PAS) for nivolumab is available, which is a simple discount of ▮▮ from the list price of £2,633. With the PAS discount, the cost per treatment cycle of nivolumab is ▮▮▮▮▮▮. There is also a PAS discount for ipilimumab of ▮▮▮▮ from the list price, the cost per treatment cycle with the PAS discount is ▮▮▮▮▮▮.

For the NIVO+IPI part of the treatment regimen, administration costs for nivolumab and ipilimumab together incur the cost of £370.68. For subsequent nivolumab monotherapy cycles, administration

costs are £241.06. Table 36 presents an overview of the drug acquisition and administration costs included in the model for the NIVO+IPI.

Table 36. Drug acquisition and administration costs for NIVO+IPI (adapted from Tables 35-36 and Tables 38 – 39 of the CS)

Treatment	Components	Acquisition cost per treatment cycle	Administration cost per treatment cycle	Total cost per treatment cycle
NIVO+IPI (treatment cycles 1-4)	Nivolumab 3mg/kg IV infusion over 30 mins every 3 weeks	£2,633 (list price) ▉ (with PAS discount)	£370.68 - Weighted average of SB14Z codes for complex chemotherapy (DCRDN; OP; Oth)[58]	£10,503.68 (list price) ▉ (with PAS discounts applied)
	Ipilimumab 1mg/kg IV infusion over 90 mins every 3 weeks	£7,500 (list price) ▉ (with PAS discount)		
Nivolumab monotherapy (treatment cycle 5 onwards)	Nivolumab 240mg IV infusion every 2 weeks (based on mean body weight of 73.7kg in CheckMate 142)	£2,633 (list price) ▉ (with PAS discount)	£241.06 - Weighted average of SB12Z codes for simple parenteral chemotherapy (DCRDN; OP; Oth)[58]	£2,874.06 (list price) ▉ (with PAS discount)

Abbreviations: CS, company submission; DCRDN, Daycase and Regular Day/Night; IV, intravenous; kg, kilogram; NIVO+IPI, nivolumab in combination with ipilimumab; OP, outpatient; Oth, other; PAS, patient access scheme.

There are four key comparators in the model, of which three incur drug acquisition costs, TRI-TIP, FOLFIRI and FOLFOX (the additional comparator is BSC). A confidential PAS for TRI-TIP is in place and cost-effectiveness results including this discount can be found in the confidential appendix.

Dosing for chemotherapy interventions is based on mean patient body surface area and weight based on patient characteristics from Checkmate 142 and is assumed to be 1.78m^2 and 73.7kg. Details of the comparator drug acquisition and administration costs are given in Table 37.

Table 37 - Comparator drug acquisition costs (adapted from Table 41 of the CS)

Drug treatment	Components	Cost per dose (list price)[61]	Cycle length	Acquisition cost per treatment cycle	Administration cost per treatment cycle	Total cost per treatment cycle
TRI-TIP	Trifluridine/tipiracil 3x20mg	£100.00	28 days	£2,000.00	£195.44 - Weighted average of SB11Z codes for oral chemotherapy (DCRDN; OP; Oth)[58]	£2,195.44
FOLFIRI	Fluorouracil (bolus) 20ml	£1.13	14 days	Cycle 1 = £22.09	£370.68 - Weighted average of SB14Z codes for complex chemotherapy (DCRDN; OP; Oth)[58]	Cycle 1 = £392.77
	Fluorouracil (IV) 100mg/50ml x2	£3.76		Cycle 2 = £24.72		Cycle 2 onwards = £395.40
	Folinic Acid 10x10ml	£5.97				
	Irinotecan 17ml	£14.99				
FOLFOX	Fluorouracil (bolus) 20ml	£1.13	14 days	Cycle 1 = £24.44	£370.68* - Weighted average of SB14Z codes for complex chemotherapy (DCRDN; OP; Oth)[58]	Cycle 1 = £395.12
	Fluorouracil (IV) 100mg/50ml x2	£3.76		Cycle 2 = £27.07		Cycle 2 onwards = £397.75
	Folinic Acid 10x10ml	£5.97				
	Oxaliplatin 2x40ml	£17.34				

Abbreviations: CS, company submission; DCRDN, Daycase and Regular Day/Night; IV, intravenous; kg, kilogram; mg, milligram; ml, millilitre; OP, outpatient; Oth, other; TRI-TIP, trifluridine/tipiracil

*A cost of £383.13 was presented in Table 41 of the CS, which is different to the value used in the economic model. As such the cost in the company's economic model is presented in this table.

4.2.10.2 Health state costs

Resource use estimates for the pre- and post-progression health states were obtained from NICE TA405[2]. Unit costs were obtained from the NHS Reference Costs schedule 2018-19[58] and the PSSRU Unit Costs of Health and Social Care[59]. More details on these unit costs (codes and descriptions) can be found in Table 45 of the CS. Table 38 summarises the resource use and cost estimates applied in the model.

Table 38. Monthly health state resource use and costs (adapted from Table 44 of the CS)

Component	Unit cost*	Pre-progression		Post-progression	
		Use	Cost	Use	Cost
Medical oncologist outpatient consultationᵗ	£197.70	0	£197.70	0	£0.00
GP home consultation	£102.79	0	£0.00	0.25	£25.70
Community nurse specialist visit	£46.00	0	£0.00	1	£47.00
Health home visitor	£46.68	0.25	£11.67	1	£46.68
District nurse visit	£46.00	0	£0.00	1	£47.00
GP surgery visit	£39.00	0	£0.00	1	£39.00
Monthly cost		£11.67		£203.38	
Weekly cost		£2.68		£46.77	

Abbreviations: GP, general practitioner.

* In line with TA405, SE assumed to be 20% of mean value

ᵗ It is assumed that only BSC patients incur one Medical oncologist outpatient consultation, in line with TA405. All other patients would be seen by clinicians during their regularly scheduled administration visit.

ERG critique

The SmPC for NIVO+IPI states that patients should be monitored for cardiac and pulmonary adverse reactions continuously and that patients should be monitored at least up to 5 months after the last dose[73]. Clinical experts also advised the ERG that they would expect patients on NIVO+IPI to require additional monitoring for immune-related AEs. In response to a clarification request the company provided a scenario where patients receive monitoring for cardiac and pulmonary adverse reactions, equivalent to one visit with a general medical doctor (£167.24), one echocardiogram (£256.61) and one lab test (£2.79) every four weeks. Adding these costs to the model had a small impact on the cost-effectiveness results. Nonetheless, the ERG considers it important to include these costs in its base case analyses to reinforce what is expected in clinical practice if NIVO+IPI is made available.

The ERG's clinical experts were also concerned that CT scans were omitted from the company's health state costs and that oncologist visits were too infrequent. During the clarification stage, the company provided several scenarios to address these concerns. However, the impact on the cost-effectiveness results was negligible.

4.2.10.3 Adverse event costs

The company included a one-off cost in each treatment arm to account for the impact of managing TRAEs in the first model cycle. The unit costs of management are summarised in Table 47 of the CS. Unit costs were obtained from the NHS Reference Costs schedule 2018-19[58], TA405[2] and Copeley-Merriman *et al.* 2018[74]. When the costs and incidence rates are combined, the expected one-off cost to manage TRAEs is £259.43 for NIVO+IPI, £122.87 for TRI-TIP, £21.83 for BSC, £53.57 for FOLFOX and £60.60 for FOLFIRI. Incidence rates have been given previously in Section 4.2.8.

ERG critique

The ERG has no major issues with the TRAE costs included in the model.

4.2.10.4 Subsequent therapy costs

In the model, patients on NIVO+IPI and comparators are switched to subsequent therapy following discontinuation, while patients in the BSC arm remain on BSC until death. The cost of subsequent therapy applied in the model was taken from TA405[2] as data in CheckMate 142 were limited for patients who had discontinued treatment or experienced a progression event. As shown in Table 42 of the CS, only ▉▉▉▉ of patients received a subsequent systemic therapy in CheckMate 142 at the Feb 2019 data cut.

The subsequent therapy cost in TA405 was estimated using the post-progression treatments received in the RECOURSE trial. However, in TA405, no details were provided around the composition of post-progression treatments, only average total costs were available (£1,528.00). This cost was inflated by the company to 2018/19 prices (£1,621.21) and applied to all treatment arms at the point of discontinuation (not progression).

As a scenario analysis, the company assumed that patients receiving NIVO+IPI, FOLFIRI or FOLFOX receive TRI-TIP as a subsequent therapy, followed by BSC. The one-off cost applied in this scenario is £8,984.56. As shown in Section 5.1.2.6, this change had a minimal impact on the cost-effectiveness results.

ERG critique

The ERG has a few concerns around subsequent therapy costs. These include when subsequent therapy is initiated, the duration of subsequent therapy and the composition of subsequent therapy. Each of these issues is described in turn below.

The ERG's clinical experts disagreed with the company's assumption that subsequent therapies are initiated immediately after the prior line is discontinued. In clinical practice, subsequent therapies are considered when there is a change in a patient's progression status (and offered upon progression). To address the clinical experts' concerns, the company was asked to provide a scenario where patients only begin subsequent therapy upon progression. In their response, the company explained that the model structure was not constructed to formally enable such an analysis. As such, an *ad-hoc* adaptation of the model was undertaken. Following these adaptations only patients that moved to the progressed health state were assumed to start subsequent therapy. Nonetheless, the impact on the cost-effectiveness results was minimal.

An additional and related area of concern is when patients receive subsequent therapy when they discontinue nivolumab treatment because of the stopping rule. In the model, if a starting cohort of 1,000 patients is considered, ■■ patients discontinue nivolumab at month 24 because of the stopping rule. Of these patients, ■■ are in pre-progression and ■ are in post-progression. However, the stopping rule doesn't enable any of these patients to incur subsequent therapy costs. The ERG considers this to be counterintuitive to the company's base case assumption that patients begin subsequent therapy upon discontinuation. As a minimum, the ERG considers that patients who have progressed should incur subsequent therapy costs (i.e. ■ patients should incur subsequent therapy costs when they discontinue nivolumab at month 24). For completeness, the ERG has provided a conservative analysis, which is in keeping with the company's base case assumption (■■ patients incur subsequent therapy costs when they discontinue nivolumab at month 24). Results of the ERG's scenario analyses are given in Section 6.3. The ERG also notes that removing the stopping rule fixes this issue with the logic of the model. The treatment stopping rule is discussed further in Section 4.2.6.

The ERG also questioned why the same one-off subsequent therapy cost (£1,621.21) was applied to all treatment arms when these treatment arms have different survival times. To address the ERG's concerns, the company provided a scenario where the one-off subsequent therapy cost is applied as a weekly cost (£69.99). This weekly cost was calculated by scaling the total cost by the weeks of post-progression survival in TA405 (23.5 weeks). This scenario also had a minimal impact on the

cost-effectiveness results, which surprised the ERG given that NIVO+IPI leads to a large PPS benefit. Upon inspection of the model used to derive these results, the ERG found that the company applied the nivolumab stopping rule to the subsequent therapy costs (i.e. after month 24 no subsequent therapy costs are incurred). The ERG disagrees with this as there is no reason for them to be connected in this scenario. For completeness, the ERG has provided results removing this stopping rule on subsequent therapy costs in Section 6.3. However, the ERG caveats this analysis with the possibility that the composition (and weekly cost) could change over time. As such, this issue would benefit from further exploration by the company.

Following this, an additional and related area of concern is the composition of subsequent therapy. Given that no details were provided around the composition of subsequent therapy in TA405[2], the composition of subsequent therapy in TA405 may be outdated. The ERG also adds that inflating the TA405 cost to a 2018/19 cost year does not address this potential issue. The company, in their response, explained that since the review of TRI-TIP in NICE TA405, no new CRC therapies have been appraised by NICE and there has been no major practice-changing research published. The company added that this is confirmed by NG151[75], published in January 2020. As such, the ERG agrees with the company that TA405 is the best available evidence to inform the one-off cost of subsequent therapies in the comparator arms.

The ERG also sought clinical expert advice to see what the composition of subsequent therapies looks like in clinical practice. Advice received by the ERG noted that TRI-TIP, regorafenib, cetuximab (with or without encorafinib), panitumumab would be considered in addition to BSC (Table 59 in Appendix 9.13). They also added that sorafenib, denosumab, trametinib and trastuzumab would not be considered. Unfortunately, no details regarding the duration of these therapies (according to each treatment arm) was received. As such, the ERG would urge the company to explore a scenario which considers the composition of subsequent therapy and duration of subsequent therapy in order to address this important area of uncertainty.

4.2.10.5 MSI testing costs

As per NICE guidance (DG27[76] and NG151[75]), the company believes that all patients should now be tested for MSI across the UK. This assumption was also validated with the company's clinical experts. Therefore, the company omitted MSI testing costs from its base case analysis.

For completeness, the company provided a scenario analysis including the cost of MSI testing. The cost of testing was derived from the cost of immunohistochemistry in DG27 (£221.95). A

conservative approach was taken, and it was assumed that no patients would receive this test in the comparator arm. This cost was applied at model initiation in the NIVO+IPI arm. As shown in Section 5.1.2.6, this change had a minimal impact on the cost-effectiveness results.

ERG critique

According to the NICE final scope[28], the economic modelling should include the costs associated with diagnostic testing for MSI in people with mCRC who would not otherwise have been tested. Based on advice from the ERG's clinical experts, the company's rationale to exclude testing costs is considered reasonable by the ERG, as assessment of MSI or dMMR is standard clinical practice for all patients with mCRC.

4.2.10.6 End of life costs

End of life costs were taken from Round *et al.* 2015[77] and applied as a one-off cost to each treatment arm in the cycle prior to death. As detailed in Table 46 of the CS, the total end of life cost in 2018/19 prices is £6,787.99, which can be subdivided into health care costs of £5,194.53 and social care costs of £1,593.46.

ERG critique

The ERG has no major issues with the end of life costs included in the model.

5 Cost effectiveness results

5.1.1 Company's cost effectiveness results

The company's pairwise results are given in Table 39. The company's fully incremental results (calculated by the ERG) are given in Table 40.

Table 39. Company's deterministic base case results, pairwise

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
TRI-TIP	16,978	0.915	0.630	■	■	■	£13,367
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	9,379	0.639	0.441	■	■	■	£14,211
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	12,176	1.314	0.884	■	■	■	£14,839
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	11,527	1.284	0.874	■	■	■	£14,930

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

Table 40. Company's deterministic base case results, fully incremental

Technologies	Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
Step 1					
BSC	£9,379	0.441	-	-	-
FOLFIRI	£11,527	0.874	■	■	£4,961
FOLFOX	£12,176	0.884	■	■	£64,900

TRI-TIP	£16,978	0.630	■	■	-£18,906*
NIVO+IPI	■	■	■	■	£13,367
Step 2					
BSC	£9,379	0.441	-	-	-
FOLFIRI	£11,527	0.874	■	■	£4,961
FOLFOX	£12,176	0.884	■	■	£64,900**
NIVO+IPI	■	■	■	■	£14,840
Step 3					
BSC	£9,379	0.441	-	-	-
FOLFIRI	£11,527	0.874	■	■	£4,961
NIVO+IPI	■	■	■	■	£14,930

*Dominated **Extendedly dominated. Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

5.1.2   Company's sensitivity analyses

5.1.2.1   Probabilistic sensitivity analysis

Results of the company's probabilistic sensitivity analysis (PSA), arising from 1,000 simulations, are summarised in Table 41. Scatterplots are presented in

Figure 19 to Figure 22, while cost-effectiveness acceptability curves (CEACs) are presented in Figure 37 to Figure 42 of the CS. Based on these analyses, the probability that NIVO+IPI is cost-effective versus Tri-TIP, BSC, FOLFOX and FOLFOX is ▉▉▉ at a WTP threshold of £50,000.

The ERG considers the parameters and respective distributions chosen for PSA, outlined in Table 48 of the CS, to be generally sound. The ERG also considers the probabilistic results to be comparable to the deterministic base-case results. A limitation of the PSA is that it takes around several hours to run.

Table 41. Company's probabilistic base case results (1,000 simulations) (adapted from Table 51 of the CS)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	▉▉	▉▉	▉▉	-	-	-	-
TRI-TIP	£17,077	0.909	0.646	▉▉	▉▉	▉▉	£13,177
Comparison B							
NIVO+IPI	▉▉	▉▉	▉▉	-	-	-	-
BSC	£9,357	0.650	0.458	▉▉	▉▉	▉▉	£14,037
Comparison C							
NIVO+IPI	▉▉	▉▉	▉▉	-	-	-	-
FOLFOX	£13,062	1.277	0.899	▉▉	▉▉	▉▉	£14,474
Comparison D							
NIVO+IPI	▉▉	▉▉	▉▉	-	-	-	-
FOLFIRI	£11,306	1.245	0.886	▉▉	▉▉	▉▉	£14,752

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI: ipilimumab; LYs: life years; NIVO: nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

Figure 19. ICER scatterplot: NIVO+IPI versus TRI-TIP (reproduced from Figure 31 of the CS)
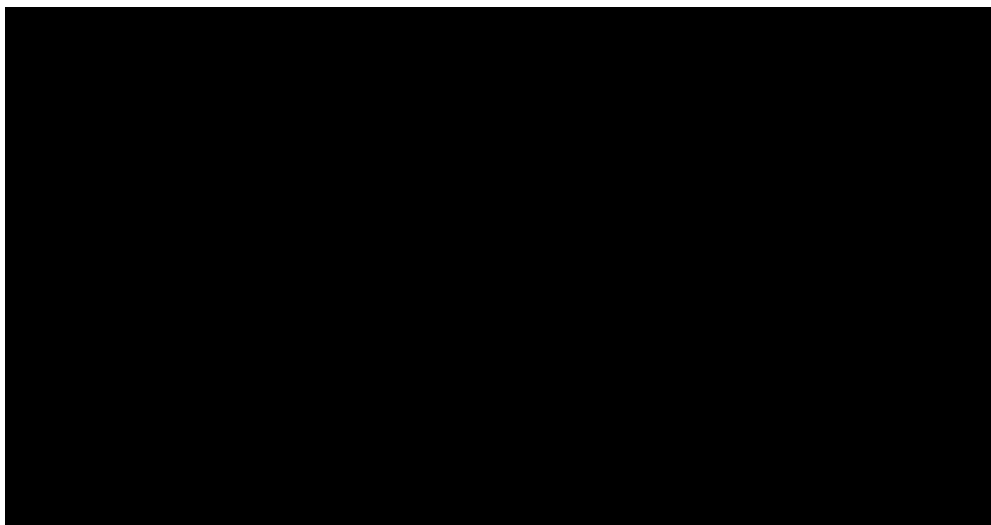
Figure 20. ICER scatterplot: NIVO+IPI versus BSC (reproduced from Figure 32 of the CS)

Figure 21. ICER scatterplot: NIVO+IPI versus FOLFOX (reproduced from Figure 33 of the CS)
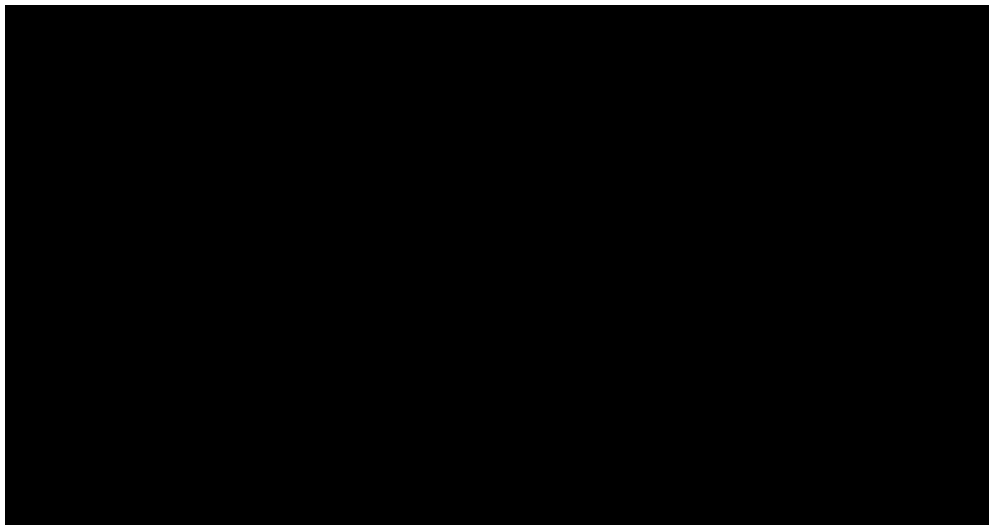
Figure 22. ICER scatterplot: NIVO+IPI versus FOLFIRI (reproduced from Figure 34 of the CS)

5.1.2.2 One-way sensitivity analysis

The company conducted a range of one-way (deterministic) sensitivity analyses, regarding the following assumption and parameters:

- Time horizon (5 and 10 years)

- Discounting: costs (0% and 6%)

- Discounting: benefits (0% and 6%)

- Baseline characteristics: age (± 20%, impacting on all-cause mortality)

- Baseline characteristics: sex (0% and 100% male, impacting on all-cause mortality)

- Health state costs: pre-progression, NIVO+IPI and comparators individually (± 20%)

- Health state costs: post-progression, NIVO+IPI and comparators individually (± 20%)

- Health state costs: death, NIVO+IPI and comparators individually (± 20%)

- Treatment costs: second line, NIVO+IPI and comparators individually (± 20%)

- Treatment costs: subsequent BSC, NIVO+IPI and comparators individually (± 20%)

- Adverse event costs (± 20%)

- Health state utility: pre-progression (for comparators), on treatment (for NIVO+IPI) (± 20%)

- Health state utility: post-progression (for comparators), off treatment (for NIVO+IPI) (± 20%)

- Proportion receiving dose, NIVO+IPI (± 20%)

- Second line adverse event prevalence, NIVO+IPI and comparators individually (± 20%)

Results are illustrated using tornado diagrams in Figure 43 to Figure 48 of the CS. The assumption that had the largest impact on the ICER was reducing the time horizon to 5 years. This analysis increased the ICER to a maximum of £40,494 (versus FOLFIRI). In all other analyses, the ICER for NIVO+IPI versus comparators remained below £20,000 per QALY.

In response to a clarification request, the company also provided results varying patient body weight. The ERG considered this to be an important analysis as NIVO+IPI are variable dose drugs based on body weight. Nivolumab is dosed at 3mg per kilogram (kg) and ipilimumab is dosed at 1mg per kg. Nonetheless, as shown in Table 42, varying patient body weight had a small impact on the results.

Table 42. One-way sensitivity analysis: impact of alternative baseline weight assumptions (adapted from Table 69 of the company's clarification responses)

Technologies	Total costs (£)	Inc. costs (£)	ICER (£/QALY)
Scenario 1: Weight -20% (58.96kg)			

NIVO+IPI	▉	-	-
TRI-TIP	£16,978	▉	£13,197
BSC	£9,379	▉	£14,046
FOLFOX	£12,176	▉	£14,661
FOLFIRI	£11,527	▉	£14,753
Scenario 2: Weight +20% (88.44kg)			
NIVO+IPI	▉	-	-
TRI-TIP	£16,978	▉	£13,537
BSC	£9,379	▉	£14,375
FOLFOX	£12,176	▉	£15,016
FOLFIRI	£11,527	▉	£15,107
Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil			

5.1.2.3 Alternative sources of comparator efficacy

The company undertook a series of scenario analyses (Table 43) to assess the impact of applying alternative efficacy evidence, these include:

1. Alternative sources of comparator data. These mean survival outcomes are taken from the MAIC, as per the base case.

2. An unadjusted analysis (a naïve comparison). These survival outcomes are derived from KM data, with survival outcomes digitised and extrapolated using parametric survival distributions.

3. A pooled set of outcomes. These survival outcomes are derived from reported median survival data identified in the SLR. These outcomes are not combined based on relative measures versus CheckMate 142 but are instead simply weighted by study size.

Table 43. Cost-effectiveness results using alternative measures of comparator efficacy (adapted from Table 48 of the company's clarification responses)

Efficacy input vs model output	Outcome	TRI-TIP	BSC	FOLFOX	FOLFIRI
MAIC base case analysis					
Source		RECOURSE EU	RECOURSE EU	CONFIRM2	VELOUR
Efficacy input	Mean PFS	4.2	2.1	4.5	6.3
	Mean OS	10.9	7.6	15.6	15.3
Model output	Inc QALYs	■	■	■	■
	Inc Costs	■	■	■	■
	ICER	£13,366	£14,211	£14,839	£14,930
1. Alternative sources of comparator data					
Source		RECOURSE US	RECOURSE US	NA	RAISE
Efficacy input	Mean PFS	3.7	1.9	NA	7.5
	Mean OS	11.7	8.1	NA	17.2
Model output	Inc QALYs	■	■	NA	■
	Inc Costs	■	■	NA	■
	ICER	£13,418	£14,240	NA	£15,183
2. Unadjusted survival outcomes (naïve comparison)					
Source		RECOURSE EU	RECOURSE EU	CONFIRM2	VELOUR
Efficacy input	Mean PFS	3.6	1.8	5.5	6.8
	Mean OS	10.4	7.2	17.3	15.7
Model output	Inc QALYs	■	■	■	■
	Inc Costs	■	■	■	■
	ICER	£13,304	£14,177	£15,056	£14,993

3. Pooled median SLR outcomes					
Efficacy input	Median PFS	2.6	1.7	4.9	4.6
	Median OS	7.9	6.1	11.9	12.7
Model output	Inc QALYs	■	■	■	■
	Inc Costs	■	■	■	■
	ICER	£13,393	£14,305	£15,117	£15,265

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYs, life years; NA, not applicable; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

5.1.2.4   Threshold analysis

In order to assess the impact of the uncertainty on the analysis, the company adjusted the mean OS for NIVO+IPI, monotonically, to derive an exponential rate for use within the economic model. Table 44 shows the mean OS and QALY gains required to be cost-effective at a £50,000 per QALY WTP threshold, with mean OS ranging from 34.2 months (versus BSC) to 43.3 months (versus FOLFIRI) and incremental QALY gains ranging from 1.349 (versus TRI-TIP) to 1.498 (versus BSC). Given that median OS has not been reached, despite median follow-up of ■ months, it is extremely likely that the mean OS for NIVO+IPI reaches the threshold to be cost-effective at a £50,000/QALY threshold, using the company's preferred assumptions.

Table 44. Threshold analysis: NIVO+IPI mean OS and incremental QALYs (adapted from Table 52 of the CS)

Technologies	NIVO+IPI mean OS required to be CE at £50,000/QALY (months)	Incremental QALYs required to be CE at £50,000/QALY
TRI-TIP	35.1	1.349
BSC	34.2	1.498
FOLFOX	43.2	1.443
FOLFIRI	43.3	1.457

Abbreviations: BSC, best supportive care; CE, cost-effective; FOLFIR, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; OS, overall survival; QALY, quality-adjusted life year; TRI-TIP, trifluridine-tipiracil

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5.1.2.5 Alternative NIVO+IPI survival extrapolations

Results using alternative NIVO+IPI survival extrapolations can be found in Tables 53 to 58 of the CS. The impact on ICERs versus the comparators ranged between £11,410 per QALY (when a semi-parametric Gompertz curve was applied for OS versus TRI-TIP) and £20,046 per QALY (when a semi-parametric exponential curve was applied for OS versus raltitrexed). However, the ERG does not consider these results to be that informative because the model was only set up to include MAIC output (relative mean survival estimates) based on the base case extrapolation for NIVO+IPI (KM to 6.44 months followed by an exponential extrapolation for PFS and a log logistic extrapolation for ToT and OS). As such, there is a disconnect between the mean NIVO+IPI survival outcome in the economic analysis and the mean NIVO+IPI survival input in the MAIC.

In response to a clarification request the company explained that it is not feasible to provide an economic model where changing the survival extrapolation for NIVO+IPI impacts the comparator outcomes automatically, as this would need to be calculated outside the model in advance and provided within the model. Instead, the company provided MAIC analyses using all extrapolations for NIVO+IPI OS and PFS for the 6.44-month semi-parametric fits (see Tables 2 to 13 in the company's additional clarification response). The company noted that although the relative treatment effect was highly variable, when these were applied to the NIVO+IPI mean survival the resultant absolute outcomes were comparable. Additionally, when these results are applied in the economic model, cost-effectiveness outcomes are relatively similar due to the large beneficial impact of NIVO+IPI. Due to time constraints, the ERG has been unable to validate these analyses and generate cost-effectiveness outcomes.

5.1.2.6 Other scenarios

The company performed a range of other scenario analyses which involved varying assumptions around the PFS endpoint, the stopping rule for nivolumab, utility values, MSI testing costs, remission and subsequent therapies. These results are summarised by the ERG in Table 45. More details can be found in Section 3.8.3 of the CS.

Table 45. Results of the company's scenario analyses

Results per patient	NIVO+IPI (1)	TRI-TIP (2)	BSC (3)	FOLFOX (4)	FOLFIRI (5)	Incremental value			
						(1-2)	(1-3)	(1-4)	(1-5)
Company base case									
Total costs (£)	■■■	16,978	9,379	12,176	11,527	■■■	■■■	■■■	■■■
QALYs	■■■	0.630	0.441	0.884	0.874	■■■	■■■	■■■	■■■
ICER (£/QALY)						13,367	14,211	14,839	14,930
Impact of BICR PFS									
Total costs (£)	■■■	16,978	9,379	12,176	11,527	■■■	■■■	■■■	■■■
QALYs	■■■	0.630	0.441	0.884	0.874	■■■	■■■	■■■	■■■
ICER (£/QALY)						13,495	14,248	14,879	14,970
Impact of removing stopping rule									
Total costs (£)	■■■	16,978	9,379	12,176	11,527	■■■	■■■	■■■	■■■
QALYs	■■■	0.630	0.441	0.884	0.874	■■■	■■■	■■■	■■■
ICER (£/QALY)						31,655	31,907	33,814	33,869
Impact of alternative utilities (NIVO+IPI utilities applied by progression status and set equal to the comparator arms)									
Total costs (£)	■■■	16,978	9,379	12,176	11,527	■■■	■■■	■■■	■■■
QALYs	■■■	0.630	0.441	0.884	0.874	■■■	■■■	■■■	■■■
ICER (£/QALY)						13,148	13,985	14,585	14,675
Impact of inclusion of testing for MSI test cost									
Total costs (£)	■■■	16,978	9,379	12,176	11,527	■■■	■■■	■■■	■■■

QALYs	■	0.630	0.441	0.884	0.874	■	■	■	■
ICER (£/QALY)						13,405	14,248	14,879	14,970
Remission in a proportion of patients*									
Total costs (£)	■	16,978	9,379	12,176	11,527	■	■	■	■
QALYs	■	0.630	0.441	0.884	0.874	■	■	■	■
ICER (£/QALY)						9,615	10,320	10,548	10,619
Subsequent therapy (TRI-TIP followed by BSC)									
Total costs (£)	■	NA	NA	16,510	18,889	NA	NA	■	■
QALYs	■	NA	NA	0.884	0.874	NA	NA	■	■
ICER (£/QALY)						NA	NA	14,526	14,613

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

* Some UK clinical experts asserted that long-term outcomes were very good in patients who were alive and pre-progression in two years. These experts described these patients as being in remission, with only a small proportion subject to ongoing hazard from CRC-related death. In line with this suggestion, an analysis was undertaken wherein 90% of patients who are alive and pre-progression at two years are assumed to be subject to general population survival and utility.

5.1.3   Model validation and face validity check

For the model validation, the company stated that a technical review of the cost-effectiveness model was conducted by an independent economist. Further, the relevance of the model structure and assumptions were validated through consultation with UK clinicians. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

The company also validated the survival extrapolation for NIVO+IPI against longer-term survival data from NIVO+IPI in other indications (melanoma, non-small cell lung cancer and renal cell carcinoma). These comparisons are given in Table 69 of the CS and show that immunotherapies are associated with prolonged survival benefits. However, the ERG's clinical experts recommended caution when

making comparisons in different indications as immune system control depends on the type of cancer which may affect the efficacy of the immunotherapies.

The company also highlighted that mean PFS in the NIVO+IPI arm is predicted to be ███ years, while post-progression survival (PPS) is predicted to be ███ years. The long PPS was considered plausible by the company for two key reasons: the PFS extrapolation is conservative, and patients who continue NIVO+IPI post progression can respond to treatment and achieve long-lasting benefits.

Although the ERG considers the company's model validation and face validity check to be robust, the ERG is concerned that it is not feasible to provide an economic model where changing the survival extrapolation for NIVO+IPI impacts the comparator outcomes (in the MAIC) automatically, as this needs to be calculated outside the economic model in advance and provided within the economic model. As such, there are unexplained discrepancies in survival outcomes between the economic models and MAIC (see Table 31). Aside from these discrepancies, the ERG has found no errors in the economic model.

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

The Evidence Review Group (ERG) has made no corrections to the company's model.

6.2 Exploratory and sensitivity analyses undertaken by the ERG

The company was asked to perform a number of scenarios during the clarification stage. These included alternative progression free survival (PFS), time on treatment (ToT) and overall survival (OS) curves, alternative matching-adjusted indirect comparison (MAIC) methods, alternative disease management costs and alternative subsequent therapy assumptions, which the company provided. However, the ERG's request to use an MAIC adjustment set using all effect modifiers or prognostic variables was not provided by the company (see Section 4.2.6.1.4). The ERG considers that this still warrants further exploration in the model. The ERG also disagrees with how the company implemented weekly subsequent therapy costs in response to clarification question (CQ) B26 and how the company omitted subsequent therapy costs from patients who discontinue nivolumab (NIVO) at month 24 (see Section 4.2.10.4).

In light of the company's clarification responses, the ERG also considers it worthwhile to explore alternative utility values for NIVO+IPI (see Section 4.2.9):

- Using ▇▇▇▇ for the first 7 weeks of NIVO+IPI treatment to reflect the high toxicity associated with ipilimumab (IPI);
- Using the utility values for NIVO+IPI on-treatment provided during the clarification stage:
  - Pre-progression on treatment 0.837;
  - Post-progression on treatment 0.728; and,
- A combination of the above.

Another key scenario the ERG would like to perform on HRQoL relates to the utility values according to progression status. As noted in Section 4.2.9 there were discrepancies between the company's values and the values reported in the CORRECT publication[1].

Finally, the ERG would like to explore a scenario where FOLFOX ToT is calculated using a mean estimate (5.1 months = exponential λ 0.136) (see Section 4.2.6.1.4).

6.3 ERG scenario analysis

Results using the MAIC "all available" adjustment set based the company's preferred survival extrapolations for NIVO+IPI and the ERG's preferred survival extrapolations for NIVO+IPI are given in Table 46. Results related to changes in utility values and subsequent therapies are given in Table 47. Table 48 provides the results using a mean estimate to calculate FOLFOX ToT.

Table 46. Results of the ERG's scenario analyses: MAIC "all available" adjustment set

Efficacy input vs model output	Outcome	TRI-TIP	BSC	FOLFOX	FOLFIRI
MAIC base case analysis (SP models using 6.44 months of KM data)					
Source		RECOURSE/EUR	RECOURSE/EUR	CONFIRM2	RAISE	VELOUR
Efficacy input	Mean PFS	4.19	2.10	4.49	7.5	6.33
	Mean OS	10.86	7.55	15.65	17.2	15.30
Model output	Inc QALYs	■	■	■	■	■
	Inc Costs	■	■	■	■	■
	ICER	£13,366	£14,211	£14,839	£15,183	£14,930
"all available" adjustment set using the company's preferred NIVO+IPI curves (SP models using 6.44 months of KM data)**					
Source		TERRA*	LUME-COLON 1*	CONFIRM2	RAISE	VELOUR
Efficacy input	Mean PFS	6.81	1.76	5.02	12.42	11.56
	Mean OS	32.22	12.18	16.76	22.66	31.82
Model output	Inc QALYs	■	■	■	■	■
	Inc Costs	■	■	■	■	■
	ICER	£15,710	£14,500	£14,963	£16,031	£17,149

"all available" adjustment set using the ERG's preferred NIVO+IPI curves (SP models using 2.99 months of KM data)***

Source		TERRA*	LUME-COLON 1*	CONFIRM2	RAISE	VELOUR
Efficacy input	Mean PFS	5.89	4.13	6.82	11.59	15.30
	Mean OS	29.74	14.29	18.29	34.09	38.52
Model output	Inc QALYs	■	■	■	■	■
	Inc Costs	■	■	■	■	■
	ICER	£15,444	£14,739	£15,235	£17,395	£18,255

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYs, life years; MAIC, matching adjusted indirect comparison; NIVO+IPI, nivolumab with ipilimumab; OS, overall survival; PFS, progression free survival; QALYs, quality-adjusted life years; SP, semi-parametric; TRI-TIP, trifluridine-tipiracil

*Company unable to provide "all available" adjustment set for RECOURSE, alternative studies used

**Calculated using the methods and values provided by the company at clarification (Tables 6 and 7 in ID1332 Nivolumab Company clarification response addendum v0.2 221220 RA [ACIC])

*** unadjusted ln(mean) values not reported for NIVO+IPI in the company's final clarification response, these have been calculated by the ERG using the company's model in response to CQ B5 and in light of the factual accuracy check (■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■)

Table 47. Results of the ERG's scenario analyses: alternative utility values for NIVO+IPI and alternative subsequent therapy cost assumptions

Results per patient	NIVO+IPI (1)	TRI-TIP (2)	BSC (3)	FOLFOX (4)	FOLFIRI (5)	Incremental value			
						(1-2)	(1-3)	(1-4)	(1-5)
Company base case									
Total costs (£)	■	16,978	9,379	12,176	11,527	■	■	■	■
QALYs	■	0.630	0.441	0.884	0.874	■	■	■	■
ICER (£/QALY)						13,367	14,211	14,839	14,930
7 week on-treatment utility value for NIVO+IPI									
Total costs (£)	■	16,978	9,379	12,176	11,527	■	■	■	■

QALYs	▮	0.630	0.441	0.884	0.874	▮	▮	▮	▮
ICER (£/QALY)						13,391	14,236	14,867	14,958

Alternative on-treatment utility values for NIVO+IPI

Total costs (£)	▮	16,978	9,379	12,176	11,527	▮	▮	▮	▮
QALYs	▮	0.630	0.441	0.884	0.874	▮	▮	▮	▮
ICER (£/QALY)						13,424	14,270	14,905	14,997

NIVO+IPI combined utility scenario

Total costs (£)	▮	16,978	9,379	12,176	11,527	▮	▮	▮	▮
QALYs	▮	0.630	0.441	0.884	0.874	▮	▮	▮	▮
ICER (£/QALY)						13,446	14,293	14,931	15,023

Alternative CORRECT HSUVs: PFS 0.74 and PD 0.59

Total costs (£)	▮	16,978	9,379	12,176	11,527	▮	▮	▮	▮
QALYs	▮	0.573	0.395	0.792	0.799	▮	▮	▮	▮
ICER (£/QALY)						15,448	16,376	17,146	17,305

Weekly subsequent therapy costs (removing the stopping rule in CQ B26)

Total costs (£)	▮	18,141	9,379	13,925	13,229	▮	▮	▮	▮
QALYs	▮	0.630	0.441	0.884	0.874	▮	▮	▮	▮
ICER (£/QALY)						18,344	19,225	19,938	20,029

Subsequent therapy costs for NIVO+IPI at the point of the stopping rule

Total costs (£)	95,535	16,978	9,379	12,176	11,527	▮	▮	▮	▮
QALYs	▮	0.630	0.441	0.884	0.874	▮	▮	▮	▮

ICER (£/QALY)	13,500	14,340	14,978	15,069

Abbreviations: BSC, best supportive care; CQ, clarification question; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; PD, progressed disease; PFS, progression free survival; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

Table 48. Results of the ERG's scenario analyses: calculating ToT for FOLFOX using a mean estimate

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
NIVO+IPI	███	███	-	-	-
FOLFOX	12,149	0.884	███	███	£14,844

Abbreviations: FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; QALYs, quality-adjusted life years

6.4 ERG preferred assumptions

Table 49 summarises the ERG's preferred assumptions and the cumulative impact these assumptions have on the incremental cost-effectiveness ratio (ICER). Table 50 provides more detail on the costs and quality-adjusted life years (QALYs) associated with these assumptions, cumulatively. As noted in Section 4.2.6.2.1, the ERG considers VELOUR and RAISE to be equally relevant sources of evidence for FOLFIRI. However, given that the source has a minimal impact on the cost-effectiveness results, only results using VELOUR (the company's base case source) are reported. Furthermore, the ERG could not produce probabilistic sensitivity analysis (PSA) ICERs for its base case as the PSA takes several hours to run and due to paucity of time and complexity of the model, some scenarios could not be integrated with the PSA.

Table 49. ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Cumulative ICER (£/QALY) NIVO+IPI vs			
		TRI-TIP	BSC	FOLFOX	FOLFIRI
Source		RECOURSE/EUR	RECOURSE/EUR	CONFIRM2	VELOUR
Unadjusted analysis (naïve comparison)	3.4 and 4.2.6.2.1	13,304	14,177	15,056	14,933
SP extrapolation of NIVO+IPI PFS using 2.99 months of KM data	4.2.6.1.4	13,445	14,314	15,206	15,141

SP extrapolation of NIVO+IPI ToT using 2.99 months of KM data	4.2.6.1.4	13,303	14,176	15,055	14,992
SP extrapolation of NIVO+IPI OS using 2.99 months of KM data	4.2.6.1.4	13,250	14,121	14,989	14,927
No stopping rule	4.2.6.1.4	34,326	34,552	37,257	36,915
ACM adjustment to ToT	4.2.7	32,456	32,735	35,290	34,970
HSUVs by progression status using the CORRECT values in TA405[2]	4.2.9	37,399	37,637	40,736	40,457
Additional monitoring for NIVO+IPI to reflect the SmPC	4.2.10.2	37,625	37,856	40,976	40,695

Abbreviations: ACM, all-cause mortality; BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; KM, Kaplan Meier; NIVO: nivolumab; OS, overall survival; PFS, progression free survival; SmPC, summary of product characteristics; SP, semi-parametric; ToT, time on treatment; TRI-TIP, trifluridine-tipiracil

Table 50. ERG's results using its preferred assumptions (cumulative)

Results per patient	NIVO+IPI (1)	TRI-TIP (2)	BSC (3)	FOLFOX (4)	FOLFIRI (5)	Incremental value			
						(1-2)	(1-3)	(1-4)	(1-5)
Company base case									
Total costs (£)	▮	16,978	9,379	12,176	11,527	▮	▮	▮	▮
QALYs	▮	0.630	0.441	0.884	0.874	▮	▮	▮	▮
ICER (£/QALY)						13,367	14,211	14,839	14,930
Unadjusted analysis (naive comparison)									
Total costs (£)	▮	16,973	9,303	12,334	11,525	▮	▮	▮	▮

QALYs	███	0.602	0.422	0.975	0.898	███	███	███	███
ICER (£/QALY)						13,304	14,177	15,056	14,933
SP extrapolation of NIVO+IPI PFS using 2.99 months of KM data									
Total costs (£)	███	16,973	9,303	12,334	11,525	███	███	███	███
QALYs	███	0.602	0.411	0.975	0.898	███	███	███	███
ICER (£/QALY)						13,445	14,314	15,206	15,141
SP extrapolation of NIVO+IPI ToT using 2.99 months of KM data									
Total costs (£)	███	16,973	9,303	12,334	11,525	███	███	███	███
QALYs	███	0.602	0.422	0.975	0.898	███	███	███	███
ICER (£/QALY)						13,303	14,176	15,055	14,992
SP extrapolation of NIVO+IPI OS using 2.99 months of KM data									
Total costs (£)	███	16,973	9,303	12,334	11,525	███	███	███	███
QALYs	███	0.602	0.422	0.975	0.898	███	███	███	███
ICER (£/QALY)						13,250	14,121	14,989	14,927
No stopping rule									
Total costs (£)	███	16,973	9,303	12,334	11,525	███	███	███	███
QALYs	███	0.602	0.422	0.975	0.898	███	███	███	███
ICER (£/QALY)						34,326	34,552	37,257	36,915
ACM adjustment to ToT									
Total costs (£)	███	16,973	9,303	12,334	11,525	███	███	███	███
QALYs	███	0.602	0.422	0.975	0.898	███	███	███	███

ICER (£/QALY)						32,456	32,735	35,290	34,970
HSUVs by progression status using the CORRECT values in TA405 (PFS 0.74 and PD 0.59)									
Total costs (£)	▇	16,973	9,303	12,334	11,525	▇	▇	▇	▇
QALYs	▇	0.546	0.376	0.877	0.822	▇	▇	▇	▇
ICER (£/QALY)						37,399	37,637	40,736	40,457
Additional monitoring for NIVO+IPI to reflect the SmPC									
Total costs (£)	▇	16,973	9,303	12,334	11,525	▇	▇	▇	▇
QALYs	▇	0.546	0.376	0.877	0.822	▇	▇	▇	▇
ICER (£/QALY)						37,625	37,856	40,976	40,695

Abbreviations: ACM, all-cause mortality; BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; KM, Kaplan Meier; NIVO: nivolumab; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; SmPC, summary of product characteristics; SP, semi-parametric; ToT, time on treatment; TRI-TIP, trifluridine-tipiracil

6.5   Conclusions of the cost effectiveness sections

Overall, the case made by the company to demonstrate the cost-effectiveness of NIVO+IPI, is considered by the ERG to be robust to alternative sources of comparator data and alternative methods used for indirect comparison. The method that had the largest impact on the ICER was the "all available" adjustment set. This analysis increased the ICER to a maximum of £17,149 (versus FOLFIRI based on VELOUR).

One of the ERG's primary concerns with the company's approach to the cost-effectiveness analysis is with the nivolumab stopping rule. The ERG considers that the 2-year stopping rule should be removed from the economic analysis as no formal stopping rule was applied during CheckMate 142. During CheckMate 142, around ▇ of patients were still on nivolumab treatment at 2 years. The ERG's clinical experts also fed back that their preference would be to continue nivolumab treatment until disease progression and not to take patients off nivolumab treatment if they are still deriving a benefit and remain progression-free at 2 years. This assumption has a large impact on the cost-effectiveness results, removing it increases the ICER for NIVO+IPI above £30,000 per QALY in each comparison.

During the clarification stage, PFS (IA and BICR) and OS outcomes from an updated data cut (Oct 2020) became available. However, PFS IA, ToT and OS extrapolations from the previous data cut (Feb 2019) were utilised in the economic analysis. The ERG agrees with the company that the updated data cut provides observed data to ████████ and supports the continued benefit of NIVO+IPI, above the model predictions. However, there is heavy censoring present at the end of the KM curves from 46 months onward and data beyond this point are highly uncertain. Clinical experts also advised the ERG that long-term projections are impossible to predict. Thus, a considerably longer follow-up period would be necessary to validate the long-term extrapolations (potentially 10 years or above).

The ERG also agrees with the company that there is an ████████████████ in the survival outcomes (INV PFS, ToT and OS) for NIVO+IPI. However, the KM cut-off point chosen by the company to represent this hazard in a semi-parametric model is too late. Based on feedback from the ERG's clinical experts and visual inspection of the KM curves, cumulative hazard plots and diagnostic plots, the effect of NIVO+IPI starts to become apparent at ████████████████████████████████████, as indicated by the company. Reducing the amount of KM data in the semi-parametric models to 3 months leads to smaller PFS benefits. However, the impact on OS and the cost-effectiveness results is minimal. .

One limitation of the company's "base case" model is that it is only set up to include MAIC output (relative mean survival estimates) using the base case extrapolation for NIVO+IPI (KM to 6.44 months followed by, an exponential extrapolation for PFS and a log logistic extrapolation for ToT and OS). To address this issue, the ERG requested the company to link the selection of NIVO+IPI extrapolations in the economic analysis with MAIC survival inputs. Although the company complied with this request, it was not feasible to provide an economic model where changing the survival extrapolation for NIVO+IPI impacts the comparator outcomes (in the MAIC) automatically, as this needs to be calculated outside the economic model in advance and provided within the economic model. The ERG also found discrepancies between the mean PFS and OS estimates between the company' base case model and MAIC, these could not be explained consistently by the company.

The ERG is also unclear why the company did not adjust ToT using an MAIC, as per PFS and OS. This is important because there is a disconnect between PFS and ToT if only one of these outcomes is adjusted.

Although alternative evidence synthesis methods have a minimal impact on the ICER, the ERG considers that, with these discrepancies and in the absence of a valid fully adjusted MAIC, an unadjusted comparison (naïve comparison) is likely to be the least biased approach to compare NIVO+IPI and the comparators as it is transparent in terms of the likely biases that exist within the comparison and the analysis itself has not introduced additional bias into the comparison.

In order to estimate QALYs, the company split utility values in the NIVO+IPI arm by treatment status (on-treatment and off-treatment). For the comparators, the company used utility values according to progression status (pre-progression and post-progression). The on-treatment utility value was estimated from CheckMate 142, while the others were taken from CORRECT[1]. The ERG has several issues with the company's approach to model HRQoL.

Firstly, during the factually accuracy check, the company explained that the health state utility values (HSUVs) were taken from TA242[71] and not the CORRECT publication as stated in the HRQoL section of the CS (Section 3.4 of the CS). The pre-progression HSUV between the two sources is similar (0.74 vs 0.75, CORRECT and TA242, respectively), but there is a large discrepancy in the post-progression HSUV (0.59 vs 0.69, CORRECT and TA242, respectively). The values identified by the ERG in the CORRECT publication were also used and accepted in TA405.[2] Additionally, the ERG for TA242 was concerned that the PD HSUV was too high. Given that patients in the NIVO+IPI arm stay in the post-progression health state for a substantially longer amount of time than patients in the comparator arms, using a higher post-progression utility value biases the results in favour of NIVO+IPI.

Secondly, clinical experts advised the ERG that they would not expect a significant difference in the HSUVs between treatments and concluded that a novel mechanism of action alone was insufficient to warrant treatment-specific utility values. They also considered the on-treatment utility value to be clinically implausible (too high). Finally, the baseline characteristics in CORRECT and CheckMate 142 differ and so combining them in the same analysis is questionable. For these reasons, the ERG considers using utility values according to progression status, from one study (CORRECT), to be more appropriate and in line with TA405.

As for costs, the ERG's main concerns are limited to the omission of NIVO+IPI specific monitoring and the modelling of subsequent therapy (including when subsequent therapy is initiated, the duration of subsequent therapy and the composition of subsequent therapy). In brief, the company applied the same one-off subsequent therapy cost (£1,621.21) to all treatment arms. As the treatment arms

have different survival times, the ERG considers this to be an unreasonable simplification and in favour of NIVO+IPI as this treatment is associated with prolonged survival. Although scaling this one-off cost to a weekly cost is one step closer to accounting for different survival times, the composition of subsequent therapy may change over time (e.g. patients may not receive active therapy during the last few months of their life). As such, the ERG has accepted the company's preferred assumption (a one-off cost in line with TA405) in the absence of more relevant data.

Finally, according to the NICE final scope,[28] the economic modelling should include the costs associated with diagnostic testing for microsatellite instability (MSI) in people with metastatic colorectal cancer (mCRC) who would not otherwise have been tested. Based on advice from the ERG's clinical experts, the company's rationale to exclude testing costs is considered reasonable by the ERG, as assessment of MSI or mismatch repair deficiency is standard clinical practice for all patients with mCRC.

7   End of Life

The company propose that NIVO+IPI meet both criteria outlined by the National Institute for Health and Care Excellence (NICE) for an end-of-life treatment. The company's assessment and ERG's comments are provided in Table 51. Mean OS for patients with previously treated mCRC was between 7 and 17 months depending on the treatment, based on the comparator studies identified by the company. That is, all are below the 24 months threshold, irrespective of comparator treatment or study chosen. The second criterion, an extension of life of more than three months, was met based on both the company's and the ERG's base case extrapolation of OS.

The company noted that a comparison of CheckMate 142 with outcomes from the overall mCRC population may be considered conservative, as outcomes may be poorer in mCRC patients with MSI-H/dMMR status. However, despite the potential underestimation of benefit, the benefit is still demonstrated to exceed 3 months.

As such, the ERG agrees with the company that NIVO+IPI meets the NICE end-of-life criteria.

Table 51. End of life considerations

NICE criterion	Company assessment	ERG comment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Based on SLR evidence and a previous NICE appraisal in the overall mCRC population (TA405), life expectancy is likely to be less than 24 months (see Section B.3.12.1 of the CS).	Mean OS on BSC using RECOURE/EUR = ▇ months in the company's base case and ▇ months in the ERG's base case. Mean OS on other comparators (company base case vs ERG base case): • TRI-TIP using RECOURSE/EUR: ▇ months vs ▇ months; • FOLFOX using CONFIRM 2: ▇ months vs ▇ months; • FOLFIRI using VELOUR: ▇ months vs ▇ months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In the company's base case analysis, it was estimated that NIVO+IPI use would result in an additional ▇ discounted QALYs and ▇ undiscounted life years versus comparators of interest (see Section B.3.12 of the CS).	Incremental mean OS benefit: • Company base case ranges from ▇ months (vs BSC using RECOURSE/EUR) to ▇ months (vs FOLFOX using CONFIRM 2); • ERG base case ranges from ▇ months (vs BSC using RECOURSE/EUR) to ▇ months (vs FOLFOX using CONFIRM 2).

Abbreviations: CS, company submission; dMMR, mismatch repair deficiency; ERG, evidence review group; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; IPI, ipilimumab; ITC, indirect treatment comparison; LYs, life years; mCRC, metastatic colorectal cancer; MSI-H, high microsatellite instability NIVO: nivolumab; OS, overall survival. QALYs, quality-adjusted life years; SLR, systematic literature review

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9 Appendices

9.1 Critique of the methods review

9.1.1 Literature searches

Systematic literature searches should aim to be as extensive as possible in order to ensure that as many of the relevant studies as possible are included in the review, albeit necessary to strike a balance between comprehensiveness and maintaining relevance of search results. The ERG considers the company's search strategies to have prioritised specificity over sensitivity, and as a result the ERG considers that relevant studies may not have been retrieved. The company refined search results using title/abstract and medical subject heading population terms related to metastatic colorectal cancer, rather than, more broadly, colorectal cancer. The ERG considers it possible that studies including people with mCRC may have referred more broadly to colorectal cancer in the titles and abstracts, or have been categorised under broader subject headings.

Furthermore, the ERG notes that some intervention terms were not consistently used across each search strategy and terms used for each comparator were not broad/sufficient. The ERG had the following concerns:

- Only free-text terms, and not medical subject heading terms, were used for interventions.
- FOLFOX was searched for as a free-text term, but other alternative related terms were not used, such as terms relating to specific FOLFOX regimens (e.g. FOLFOX6 or FOLFOX-6). As an example, the ERG conducted preliminary searches and notes that using terms related to FOLFOX6/FOLFOX-6 retrieved additional records not captured by FOLFOX alone.
- Terms used for FOLFIRI included the individual components within the chemotherapy ('fluorouracil AND folinic acid AND irinotecan') but terms for FOLFOX did not. Furthermore, 'fluorouracil', a drug within both FOLFOX and FOLFIRI chemotherapy, was not searched for individually. Given that these therapies may be referred to by an individual drug within each technology (e.g. 'fluorouracil-based chemotherapy'), this could have resulted in relevant studies not being retrieved. Other components of the therapies (e.g. folinic acid, capecitabine) were not searched for as individual search terms.
- Brand names for drugs were not consistently searched for
- Terms used for BSC included only 'best supportive care', 'supportive care' and 'placebo'. These may not have been sufficient, with it possible that other terms may have retrieved additional, relevant results (e.g. terms related to palliative care, end of life, no treatment).

The company also searched by study outcome. That is, the searches included medical subject heading terms for outcomes, excluding trials that were not categorised within the relevant outcome subject headings (e.g., overall survival). Searching for outcomes is often not recommended, given that outcomes may not be well defined or consistently reported in titles or abstracts, and thus relevant studies may not be captured. Although it may sometimes be appropriate to search for outcomes (e.g., if outcomes are particularly well defined), this approach would only be sufficient if using a combination of free-text and medical subject heading terms. The company only used medical subject heading terms for outcomes, and so this could have resulted in missed studies.

9.1.2 Tool for quality assessment of included study or studies

The ERG notes that, other than for CheckMate 142, only an overview of risk of bias was provided for the included studies, rather than individual quality ratings for each study. The ERG further notes that it appears only RCTs identified by the company were assessed for quality, whereas the quality of non-randomised studies identified were not evaluated. The company used the Cochrane Collaborations tool for assessing risk of bias in randomised trials,[78] and reported that among the 66 RCT publications identified in the previously treated mCRC population, 25 were judged to be low risk, 39 as unclear risk and 2 as high risk.

The ERG considers that outcomes from the RCTs should have been assessed as single-arm data, given that only data from one arm of each trial was used, and so randomisation was effectively broken. Nonetheless, most of these studies were not included in the MAIC and were therefore not informing the cost-effectiveness base case results. In order to better inform interpretation of the MAIC results, and given that each indirect comparison consists of data from single arms of two separate studies, the ERG considers that risk of bias assessment should take into account both studies included in each comparison of the MAIC. Differences between CheckMate 142 and the comparator studies which may bias the comparisons are discussed in Section 3.4.1.

9.2   Baseline characteristics – CheckMate 142

Table 52. Baseline characteristics CheckMate 142[3, 40, 79](reproduced from CS Table 9)

		NIVO+IPI
Number of patients		119
Median age, years (range)		58 (21–88)
Age, years, n (%)	<65	81 (68.1)
	≥65	38 (31.9)
Gender, n (%)	Male	70 (58.8)
Race, n (%)	White	110 (92.4)
	Black or African American	2 (1.7)
	Asian	3 (2.5)
	American Indian or Alaska Natives	1 (0.8)
	Other	3 (2.5)
ECOG*, n (%)	0	54 (45.4)
	1	65 (54.6)
Disease stage at initial diagnosis**, n (%)	II	14 (11.8)
	III	52 (43.7)
	IV	53 (44.5)
Primary tumour location, n (%)	Right colon	65 (54.6)
	Left and sigmoid colon	30 (25.2)
	Transverse colon	15 (12.6)
	Rectum	6 (5.0)
	Colon, NOS	3 (2.5)
Number of prior systematic regimens received, n (%)	0***	1 (0,8)
	1	27 (22.7)

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	2	43 (36.1)
	≥3	48 (40.4)
Prior regimens received, n (%)	5-FU (fluorouracil, capecitabine)	118 (99.3)
	Oxaliplatin	111 (93.2)
	Irinotecan	87 (73.1)
	VEGF inhibitors (bevacizumab, aflibercept, ramucirumab)	68 (57.1)
	EGFR inhibitors (cetuximab, panitumumab)	35 (29.4)
	Regorafenib	11 (9.2)
	Trifluridine-tipiracil	2 (1.7)
	Other experimental drugs	3 (2.5)
	Other chemotherapy	8 (6.7)
	5FU-Oxa-Iri	82 (68.9)
Mutation status, n (%)	Both BRAF and KRAS wildtype	31 (26.1)
	BRAF mutation	30 (25.2)
	KRAS mutation	44 (37.0)
	Unknown	14 (11.8)
Tumour PD-L1 expression quantifiable at baseline, n (%)	≥1%	27 (26.5)
	<1%	75 (73.5)
	Unknown	17 (14.2)
Lynch syndrome****, n (%)	Yes	35 (29.4)
	No	35 (29.4)
	Unknown	49 (41.2)

*One patient had an ECOG performance status of 1 at randomisation that deteriorated to 3 by the time of treatment initiation.

**All patients (n=119) were disease stage IV at study entry

***One patient was allowed to enrol after refusing any cytotoxic chemotherapy.

9.3   PFS as assessed by BICR - CheckMate 142

Figure 23. BICR-assessed progression-free survival: February 2019 database lock[40] (reproduced from CS, Figure 7)

BICR: blinded independent central review; NA: not available.

9.4 Updated outcomes from CheckMate 142 (October 2020)

In the updated data cut, ▉ of 119 patients receiving NIVO+IPI had experienced an OS event (Figure 24) demonstrating that OS outcomes are ▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉▉, with median OS ▉▉▉▉▉▉▉▉▉▉. Similarly, only ▉ patients had experienced a PFS event (per investigator [Figure 25] and per BICR [Figure 26]), so that median PFS was ▉▉▉▉▉▉▉ per investigator and was ▉▉▉▉▉▉▉ per BICR.

Figure 24. CheckMate 142 updated overall survival (reproduced from Figure 1 of company clarification responses)
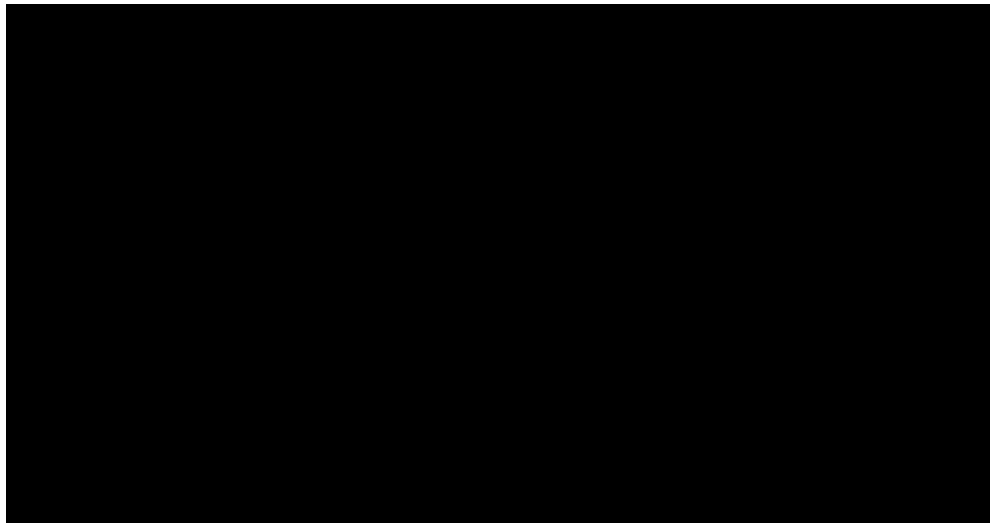
Figure 25. CheckMate 142 updated progression-free survival per investigator (reproduced from Figure 2 of company clarification responses)
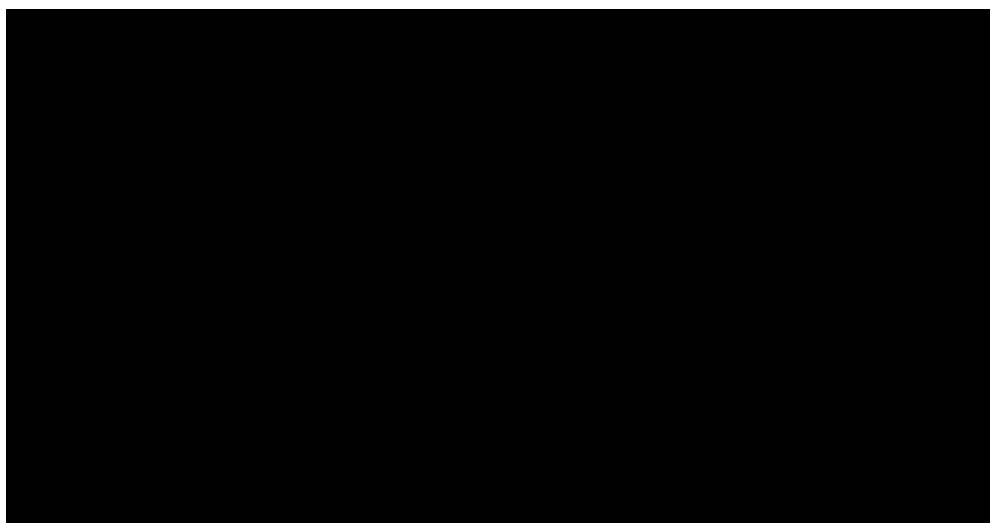
Figure 26. CheckMate 142 updated progression-free survival per BICR (reproduced from Figure 3 of company clarification responses)
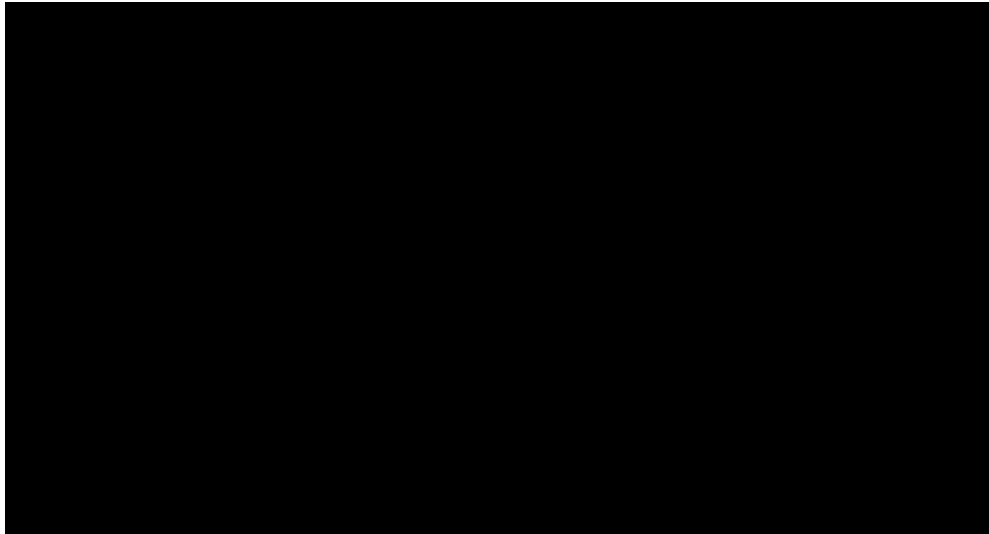
Figure 27. Comparison of modelled OS extrapolations versus CheckMate 142 updated database lock (reproduced from Figure 4 of the company's clarification responses)
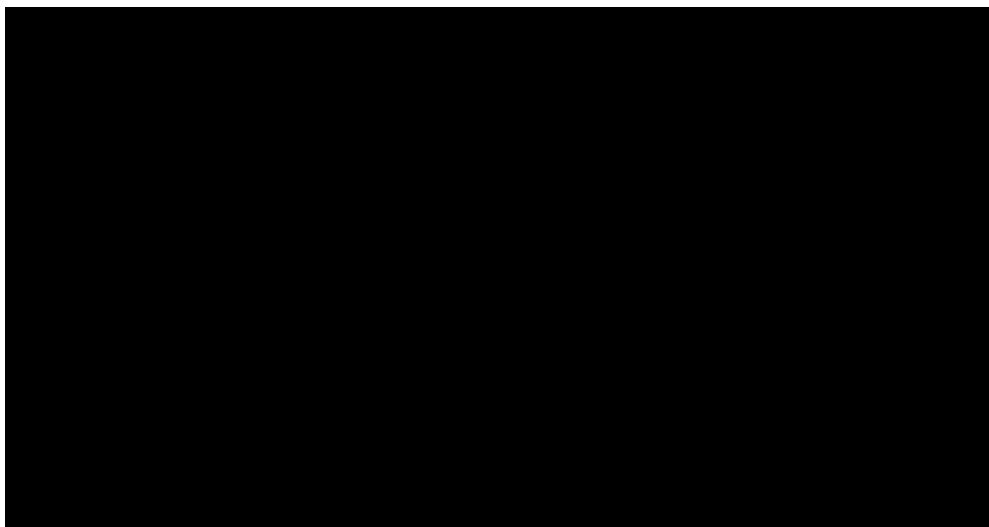
Figure 28. Comparison of modelled PFS extrapolations versus CheckMate 142 updated database lock (reproduced from Figure 5 of the company's clarification responses)

9.5   Pre-specified subgroup analyses - CheckMate 142

Table 53. CheckMate 142: Subgroup analysis of ORR by baseline characteristics[3, 40 57] (reproduced from CS, Table 12)

Stratification factor	ORR			
	BICR assessment		Investigator-assessed	
	n/N (%)	95% confidence interval[a]	n/N (%)	95% confidence interval[a]
Age				
<65 years	██████	██████	█████	█████
≥65 years	██████	████	█████	█████
≥65 and <75 years	█████	████	█████	█████
≥75 years	████	████	█████	████
Gender				
Male	█████	█████	█████	█████
Female	█████	█████	█████	█████
Region				
US/Canada	█████	████	█████	█████
Europe	█████	█████	█████	█████
Rest of world	████	█████	█████	█████
Race				
White	█████	█████	██████	█████
Lynch syndrome				
Yes	█████	█████	██████	██████
No	█████	█████	██████	█████
Unknown	█████	█████	██████	██████
KRAS/BRAF mutation status				
KRAS/BRAF wild type	█████	█████	██████	█████
BRAF mutation	█████	█████	██████	█████
KRAS mutation	█████	█████	██████	█████

Unknown	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Baseline ECOG performance status				
0	▐▐▐	▐▐▐	▐▐▐	▐▐▐
≥1	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Time from initial diagnosis				
<1 year	▐▐▐	▐▐▐	▐▐▐	▐▐▐
1≤2 years	▐▐▐	▐▐▐	▐▐▐	▐▐▐
2<3 years	▐▐▐	▐▐▐	▐▐▐	▐▐▐
≥3 years	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Primary tumour location				
Rectum	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Left and sigmoid colon	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Right colon	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Transverse colon	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Number of prior systemic regimen received				
1	▐▐▐	▐▐▐	▐▐▐	▐▐▐
2	▐▐▐	▐▐▐	▐▐▐	▐▐▐
3	▐▐▐	▐▐▐	▐▐▐	▐▐▐
>=4	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Time from completion of most recent prior therapy regimen to treatment				
< 3 months	▐▐▐	▐▐▐	▐▐▐	▐▐▐
3-6 months	▐▐▐	▐▐▐	▐▐▐	▐▐▐
>6 months	▐▐▐	▐▐▐	▐▐▐	▐▐▐
Time from progression of most recent prior therapy to treatment				
< 3 months	▐▐▐	▐▐▐	▐▐▐	▐▐▐

3-6 months	███████	███████	███████	███████
>6 months	███████	███████	███████	███████

Table 54. CheckMate 142: Response by PD-L1 expression group[40] Table 55. CheckMate 142: Response by PD-L1 expression group[40] (reproduced from CS, Table 13)

	Response by PD-L1 expression group			
	BICR assessment		**Investigator-assessed**	
	≥1% (n=27)	**<1% (n=75)**	**≥1% (n=27)**	**<1% (n=75)**
ORR, % (95% CI)	████████	████████	████████	████████
CR, %	██	██	██	██
PR, %	██	██	██	██
PFS*, months (95% CI)	██████	████████	██████	██████████
OS*, months (95% CI)	▌	▌	██████	██████

9.6 Safety data - CheckMate 142

Table 56. CheckMate 142: extent of exposure to study drugs (February 2019 DBL) (reproduced from CS, Table 17)

Variable	All patients N=119	
	Nivolumab	**Ipilimumab**
Number of doses received		
Mean (SD)	███████	███████
Median (Range)	██████	█████
Cumulative dose (mg/kg)		
Mean (SD)	███████	██████
Median (Range)	█████████	███████
Relative dose intensity (n)		
≥110%, n (%)	█	█
90–110%, n (%)	█████	██████
70–90%, n (%)	█████	█████
50–70%, n (%)	████	████
<50%, n (%)	█	█

Abbreviations: SD, standard deviation

Table 57. CheckMate 142: All-cause AEs and treatment-related AEs (derived from B.2.10.1.2, B.2.10.1.3, B.2.10.1.6 in addition to Table 18 in the CS)

Total adverse events	Any grade (%)	Grade 3-4 (%)	Grade 5 (%)
All-cause adverse events			

Total patients with an event	▮	▮	NR
Serious adverse events	▮	▮	NR
AEs leading to discontinuation	▮	▮	NR
Treatment-related adverse events			
Total patients with an event	▮	▮	▮
Serious adverse events	▮	▮	▮
AEs leading to discontinuation	▮	▮	▮
Fatigue*	▮	▮	▮
Rash*	▮	▮	▮
Diarrhoea*	▮	▮	▮
Transaminases increased*	▮	▮	▮
Pruritus*	▮	▮	▮
Hypothyroidism*	▮	▮	▮
Pyrexia*	▮	▮	▮
Hyperthyroidism*	▮	▮	▮
Nausea*	▮	▮	▮
Lipase increased *	▮	▮	▮
Decreased appetite*	▮	▮	▮

Anaemia*	███	███	▮

TRAEs events were assessed during treatment and for up to 30 days after the last dose of study treatment according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

*Reported in ≥10% of patients.

Abbreviations: TRAE, treatment-related adverse event.

Table 58. CheckMate 142: AESIs[40] (adapted from CS, Table 19)

	Any grade n (%)	Grade 3-4 n (%)
All-cause AESI		
Skin	██	NR
Gastrointestinal	██	NR
Hepatic	██	NR
Treatment-related AESIs		
Skin	███	██
Endocrine	███	██
Gastrointestinal	███	██
Hepatic	███	███
Pulmonary	██	██
Renal	██	██
Hypersensitivity/infusion reactions	██	██

Abbreviations: AESI, adverse event of special interest

9.7 Selection criteria for identifying studies for ITC

In order to identify the most robust and comparable data source for each comparator, the company considered the following factors:

- Study design;
  - o Clinical trial evidence (i.e. not observational studies), preferably randomised controlled trials;
  - o Studies pivotal to marketing authorisation;
  - o Previous submission to NICE;
- Population overlap, with preference given to patient populations similar to the CheckMate 142 NIVO+IPI population;
- Study size, with preference given to larger patient populations;
- Availability of survival outcome data.

Subgroup analyses were preferentially avoided, unless they resulted in a population with improved overlap with CheckMate 142; i.e. the patients excluded by the subgroup analysis had characteristics not represented in CheckMate 142.

The ERG asked for clarification around the selection factors, how they had been applied and for specific rational/criteria for the selection of each comparator study and for the exclusion of each other plausible comparator studies. The ERG also requested a re-assessment of the comparator studies prioritising availability of KM survival data but placing a greater weight on studies reporting patient characteristics for important prognostic factors such as BRAF/KRAS status. The ERG suggests not to limit the selection to studies informing NICE submissions or marketing authorisations as this would have no clear or direct impact on study quality, applicability or overlap with CheckMate 142. In addition, if there was no clear rationale for using one study over others available for a specific comparator, the ERG suggested the company use the study with the best outcomes for the comparator as this will provide a conservative estimate of the relative treatment effect versus NIVO+IPI.

9.8 Pooled analysis

The company presents analyses where a pooled estimate of all studies for each comparator is compared with a pooled estimate of the two NIVO+IPI studies (CheckMate 142 and NIPICOL) identified in the company's SLR. The company presented weighted average median and weighted

mean PFS and OS and pooled baseline characteristics (a mean weighted by patient numbers) for each intervention, with outcomes weighted by patient numbers for each study (CS Section B.2.9.1.). A summary of the included studies is provided in the CS Appendix D.

The ERG does not consider these analyses informative as a pooled comparator estimate is likely to be for a population which is less like CheckMate 142 than the most similar individual study, thereby increasing bias compared with using the most relevant single study. The company acknowledges that it is more appropriate to conduct an adjusted comparison versus a single study than to adjust all studies and pool the results, but they still presented results for unadjusted pooled analyses.

The ERG note that the pooled analyses may be limited by the following issues:

- All relevant studies may not have been retrieved in the company's SLR and included in the pooled analyses (see Section 3.1), and it is unclear from the CS and relevant appendices how many and which studies were included for each comparator;
- An assessment of how similar or different all the individual study populations are from the NIVO+IPI studies is not provided. CS Appendix L includes description and comparison of the individual comparator studies chosen for the company base case, and at the clarification stage the company provided more details about the subset of included studies which were RCTs with available Kaplan-Meier (KM) data (clarification question A11). In addition, the company reports a summary of the quality assessment across RCTs but not for non-randomised studies (CS, Appendix D, Section 2.5) or for individual studies included in the pooled analyses;
- No sensitivity analyses were provided exploring the impact of including e.g. studies with a population more or less similar to CheckMate 142.

9.9   Spline-based models

The ERG disagrees with the company's decision to omit spline-based models from decision making because KM data from CheckMate 142 for PFS and ToT are incomplete. Firstly, the term "incomplete" is subjective as there are no requirements for a spline-based model to have "complete" data. Secondly, the company has shown that PFS and ToT have ▮▮▮▮▮ hazard functions which cannot be modelled accurately using standard parametric distributions. Thirdly, there appears to be more than one ▮▮▮▮ in the hazard profile for PFS

(███). For these reasons, the company was asked to explore spline-based models for PFS and ToT during the clarification stage.

In their response, the company stated that the KM data was associated with a clear structural discontinuity and that smoothing the hazard function would result in poor long-term performance. Nonetheless, the company assessed the placement of 0 to 7 internal knots. For each model with internal knots, the location and value of these knots was optimised by a 2-step optimisation procedure. The location of the knots was free to vary within the limits of time domain of the observed event data for the optimal placement to be achieved. Within each optimisation step, the location of the knots was varied and the knot values fitted by maximum likelihood, attempting to find the global maximum likelihood set of knot location and values. The models produced were examined for physical plausibility (e.g. hazards positive at all times) and of the plausible models (in line with TSD 14[55] guidance on fit), the best fitting was selected, considerate of overfitting by AIC. Following this, the best fitting models for PFS and ToT had 2 internal knots.

The ERG does not understand what is meant by a clear structural discontinuity. If the company means there are ███████████ in the hazard within a short period of time this would suggest spline-based models are worth considering because they are flexible enough to capture these ██████ in the hazard. Nonetheless, the ERG considers the company' methodology to implement spline-based models to be generally sound.

For PFS, the ERG considers that the ████████ hazards are sufficiently well modelled in the curve, as well as providing a plausible extrapolation to predict PFS beyond the trial period (Figure 29). However, the ERG is aware that the spline-based model is associated with a poor AIC fit statistic (447.28 compared with 290.15 for the semi-parametric model with 2.99 months of KM data and 219.76 for the semi-parametric model with 6.44 months of KM data).

Compared to the base case analysis, a spline-based model reduced the mean and median PFS time (including ACM) from ████████████████████████ to ██████████████████████, respectively. As noted earlier, the company provided the MAIC output needed to link survival extrapolations in the economic analysis with the MAIC following another round of clarification. These MAIC outputs are summarised by the ERG in Section 3.4.4. Cost-effectiveness results using a spline-based model are discussed in Section 4.2.6.1.4.

Figure 29. Spline model for NIVO+IPI IA PFS for CheckMate 142 (reproduced from Figure 38 of the company's clarification responses)
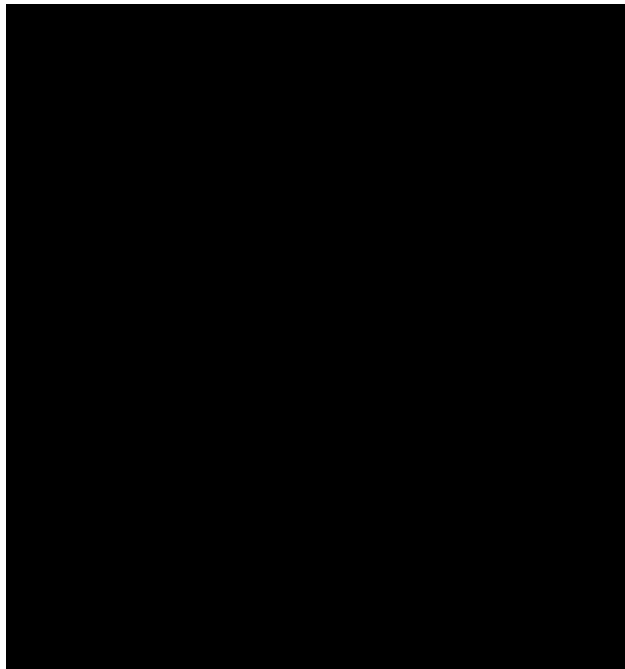
For ToT, the ERG considers the 2-knot spline model for ToT to be a very poor fit to the KM data (Figure 30). Given that the hazard profiles for PFS and ToT are not ▓▓▓▓▓▓▓▓▓▓, the ERG is surprised that this ▓▓▓▓▓▓▓▓ is not followed through into the spline-based models. To address this issue, the company was asked to explain why there are no visible knots for ToT or re-evaluate the number or location of the knots for ToT to better reflect the KM data.

In their response, the company noted that the PFS curve applied a knot in the latter period of the data, reflecting a ▓▓▓▓▓▓ the hazard profile later in the data. By contrast, the time on treatment curve applies ▓▓▓▓▓▓ knots, reflecting a more ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓. Hence, although the hazard profiles for PFS and ToT are ▓▓▓▓▓, there are underlying differences that should also be reflected when modelling the data.

The ERG appreciates the company's explanation but actually considers the company's explanation to contradict their decision to represent the ▓▓▓▓▓▓▓▓ hazard for ToT using 6.44 months of KM data. As the ▓▓▓▓▓▓▓▓ hazard appears ▓▓▓▓▓▓▓▓▓▓ before 6.44 months, a smaller amount of KM data can be used to represent it (i.e. 2.99 months).

Figure 30. Spline model for NIVO+IPI ToT for CheckMate 142 (reproduced from Figure 39 of the company's clarification responses)
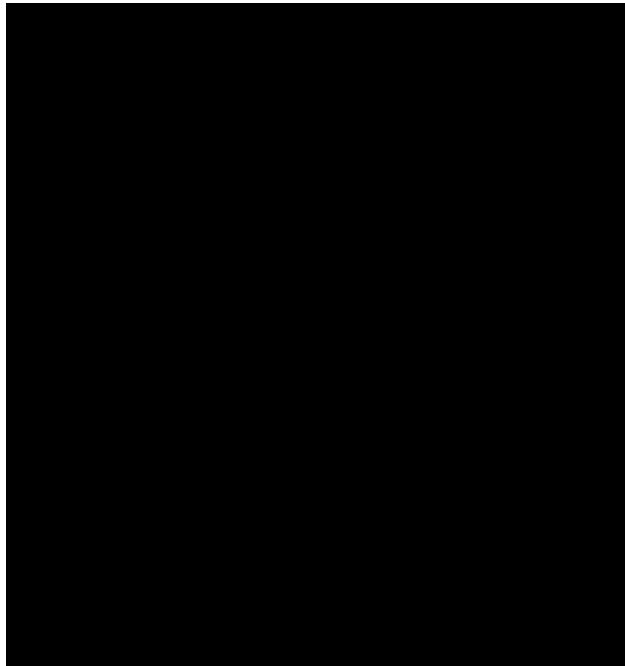
9.10 Fully parametric model for OS

Compared to PFS, there are fewer events in the tail of the OS curve to inform the extrapolation. As noted in TSD 21[65], this is a particular issue in later sections of the curve, where patient numbers at risk may be very small and the number of observed events may be low, leading to large standard errors and uncertainty when fitting survival models. Additionally, log-logistic models can represent hazards that ███████████████████ (see Section 4.2.6.1). Therefore, the ERG considers a fully parametric model using the log logistic distribution to be a reasonable scenario analysis. Compared to the base case analysis, a fully parametric log-logistic model reduced the mean and median OS time (including ACM) from ██████████████████████ to ████████████████████, respectively. Cost-effectiveness results including a fully parametric extrapolation are discussed in Section 4.2.6.1.4 and Section 5.1.2.5.

9.11 Ishak plots

Figure 31. CheckMate 142 NIVO+IPI IA PFS Ishak diagnostic plots (reproduced from Figure 3 of Appendix M)
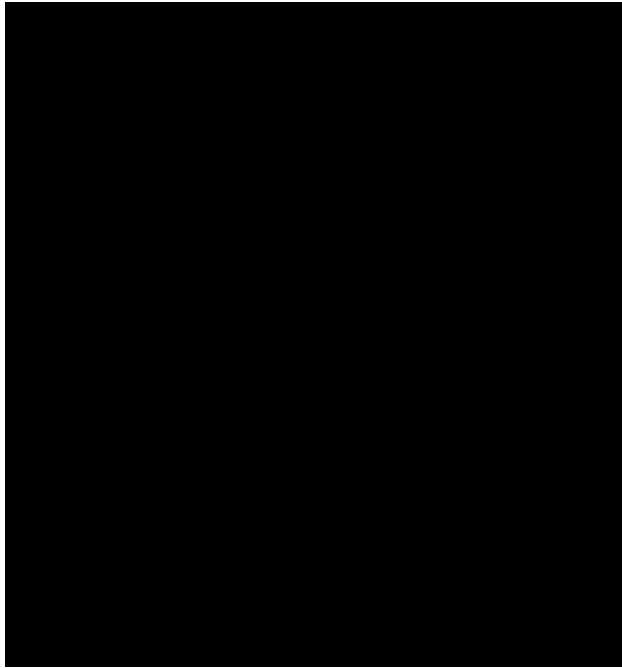
Figure 32. CheckMate 142 NIVO+IPI ToT Ishak diagnostic plots (reproduced from Figure 26 of Appendix M)
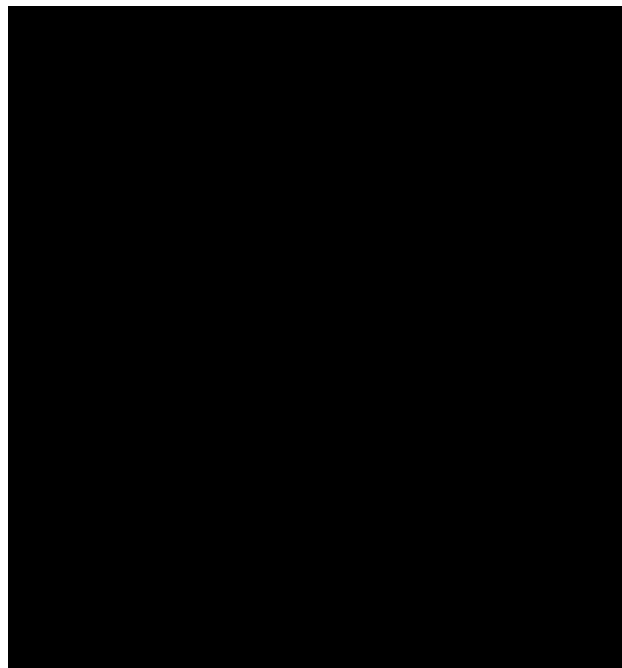
Figure 33. CheckMate 142 NIVO+IPI OS Ishak diagnostic plots (reproduced from Figure 14 of Appendix M)
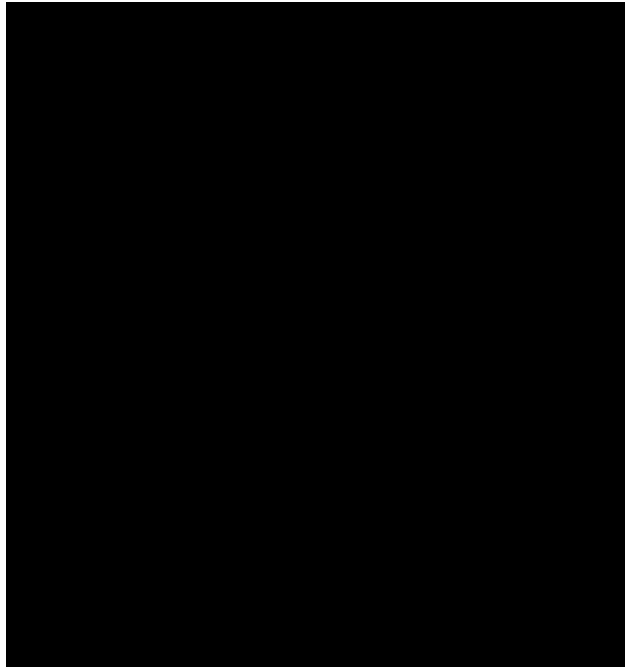
9.12 Smoothed estimators of the hazard function

Figure 34. CheckMate 142 NIVO+IPI IA PFS smoothed hazard function estimates (reproduced from Figure 4 of Appendix M)
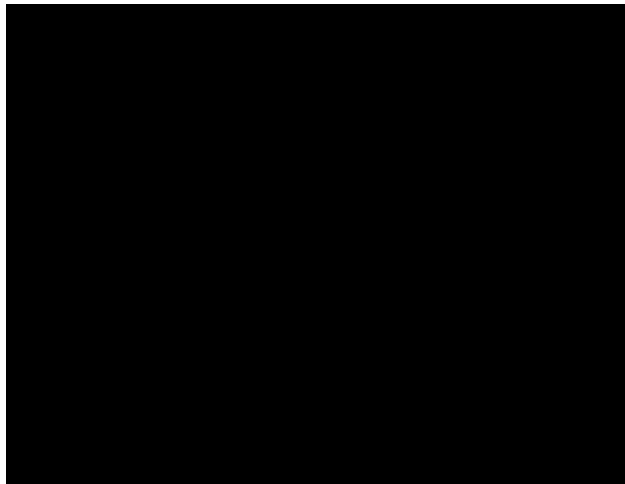
Figure 35. CheckMate 142 NIVO+IPI ToT smoothed hazard function estimates (reproduced from Figure 27 of Appendix M)

9.13 Subsequent therapies

Table 59. Distribution of subsequent therapies suggested to the ERG

3rd+ line treatment	2nd line treatment				
	NIVO+IPI	TRI-TIP	FOLFOX	FOLFIRI	BSC
TRI-TIP	30%	-	30%	30%	-
Regorafenib	20%				-
Cetuximab	If not given first line already, RAS wildtype 50% and RAF mutant with encorafinib 20%				-
Panitumumab	If not given first line already, RAS/ RAF wildtype 50%				-
BSC	100%				

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; IPI, ipilimumab; NIVO: nivolumab; TRI-TIP, trifluridine-tipiracil

9.14 Other cost-effectiveness results

Table 60. Cost-effectiveness results based on updated MAIC (adapted from Tables 37 and 39 of the company's clarification response to CQ A11)

Comparator	Study	ICER (£/QALY)
TRI-TIP	RECOURSE EUR	£13,783
	RECOURSE USA	£13,435
	TERRA*	£13,133
BSC	RECOURSE EUR	£14,428
	RECOURSE USA	£14,177
	LUME-Colon-1	£14,339
	TERRA*	£14,101
FOLFOX	CONFIRM 2	£14,793
	NO16967	£14,670
	CAPRI-GOIM*	£15,619
FOLFIRI	VELOUR	£15,810
	RAISE	£15,379

	NCT01479465**	£18,457

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

* Reflects the most optimistic outcomes for comparators

** Includes an exclusively KRAS mutant population and small patient numbers; however, used as a scenario as reflects most optimistic outcomes for comparator.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 3 February** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all <u>confidential information</u>, and separately highlight information that is submitted as '███████████████' in turquoise, all information submitted as '██████████████' in yellow, and all information submitted as '████████████' in pink.

Issue 1   Application of semi-parametric 2.99 month cut point in ERG base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
ERG base case There has been a misunderstanding in the additional survival models provided in the Clarifications Questions response. The responses provided for clarification questions B4 and B5 reflect the outcomes specified in the questions – i.e. OS, PFS and ToT - and do not reflect the same disease-specific excess hazard method of modelling survival outcomes as other models provided to the ERG. Hence, this reflects double counting of mortality events when applied with additive ACM. This was not adequately labelled in the initial CQ responses. These survival curves have been carried through to the ERG base case, which uses the same semi-parametric model as those provided in B4 and B5. This issue is reflected in the ERGs question reflected in Table 27 (i.e. the difference between the initial CQ model and the final CQ model), as the final CQ model includes excess hazard adjustment.	The company has provided an updated version of the ERG base case reflecting the excess hazard adjusted survival models.	The ERG has rightly noted the discrepancy between the initial CQ model and the final CQ model. The cause of this discrepancy is the application of disease-specific excess hazard adjustment in the final CQ models but not the initial CQ models, which was not adequately signposted.	The ERG thanks the company for highlighting this issue. The ERG is of the opinion that columns J, K and L in the worksheet 'Outcomes Trace' represent extrapolated CheckMate 142 data for PFS, OS and ToT, respectively, without any ACM adjustments. ACM adjustments are applied in columns N and O for PFS and OS, respectively. If the data in columns J, K and L include ACM in the company's response to B4 and B5, the ERG agrees that double counting of mortality will occur in columns N and O. The ERG does, however, disagree with the company's description of the problem. The ERG believes the company made an error and inserted the data into the wrong column in the worksheet. Based on the identified error, the cost-effectiveness results provided by the company in response to B4 and B5 would also be incorrect. Additionally, the information in the ERG report in the following locations is incorrect: page 69, page 86, page 108, page 180, page 183, Table 4, Table 17, Table 46, Table 51, Figure 16 and Figure 17. The ERG has updated its base case analyses using the model provided by the company. The ERG has also removed the issue in Table 27 and made the necessary amendments to the aforementioned locations.

Issue 2   Clinical evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
p. 43 3.1 Critique of the methods review The ERG states there were 194 unique studies out of the 336 publications identified in the clinical SLR. However, this is the incorrect number of identified publications.	This sentence needs to be amended to say that the clinical SLR identified 366 publications.	In the CS (B.2.1.1. Systematic literature review) and Appendix D it is stated 366 publications were identified in the clinical SLR.	The ERG thanks the company for highlighting this error. The ERG report has been amended.
p. 46 Table 14 Summary of CheckMate 142 methodology and p. 49 The ERG states: "It is unclear from the CS if there were any dropouts, i.e. withdrawal of consent during the study." The ERG further states "… company has not provided a patient flow diagram or other information around the number of patients who received the wrong dose, withdrew consent, were lost to follow up or stopped treatment for other reasons."	These statements should be removed/rephrased.	In the CS, Table 11, shows patient disposition, including those continuing and not continuing in the treatment and study periods (with reasons for discontinuation). The CS also details discontinuations due to AEs in Section B.2.10.1.6	Not a factual inaccuracy. No change required. Table 11 in the CS provides information about patients who continued or discontinued treatment but not about withdrawal of study consent.
p. 88 ERG comment on the company's review of cost effectiveness evidence The ERG states **"**Searches were initially run in August 2017 and were last updated in January 2020", which are incorrect dates.	This sentence should say "Searches were initially run in January 2017 and were last updated in August 2020"	As described in Appendix G, CEM SLR searches were initially run in January 2017 and updated in August 2020.	The ERG thanks the company for highlighting this issue. The ERG report has been amended.
p. 163 Section 9.1.1 Literature searches The ERG states "'FOLFOX', or any related	This sentence should be removed/rephrased.	FOLFOX was searched for in PubMed and the Cochrane library but was not included in the search strategy tables	The ERG thanks the company for providing the additional information. The

terms, were not searched for in PubMed nor the Cochrane Library even though FOLFOX is a key comparator listed in the NICE final scope.", which is not the case as it was included.		in Appendix D. This is an error for which the company would like to apologise for. The correct search string for interventions in PubMed was: irinotecan[Title/Abstract] OR FOLFIRI[Title/Abstract] OR LONSURF[Title/Abstract] OR (trifluridine[Title/Abstract] AND tipiracil[Title/Abstract]) OR "trifluridine-tipiracil"[Title/Abstract] OR nivolumab[Title/Abstract] OR Opdivo[Title/Abstract] OR ipilimumab[Title/Abstract] OR Yervoy[Title/Abstract] OR raltitrexed[Title/Abstract] OR tomudex[Title/Abstract] OR 'best supportive care'[Title/Abstract] OR 'supportive care'[Title/Abstract] OR placebo[Title/Abstract] OR **"FOLFOX"[Title/Abstract]"** and for the Cochrane library: irinotecan OR FOLFIRI OR LONSURF OR (trifluridine AND tipiracil) OR "trifluridine-tipiracil" OR nivolumab OR Opdivo OR ipilimumab OR yervoy OR raltitrexed OR tomudex OR 'best supportive care' OR 'supportive care' OR placebo OR **FOLFOX**):ti,ab,kw	report has been updated by removing the query about the lack FOLFOX search terms.
p. 175 Table 57 CheckMate 142: All-cause AEs and treatment-related AEs (adapted from CS, Table 18) The ERG states this table is adapted from Table 18 in the CS, however, results	To be accurate, the table caption should state the data reported in Table 57 is derived from B.2.10.1.2, B.2.10.1.3, B.2.10.1.6 in addition to Table 18 in the CS.	Data represented in this table is derived from various sections in the CS.	The ERG thanks the company for highlighting this issue. The table caption has been updated.

presented in this table are derived from various sections in the CS.			
p. 176 Table 57 CheckMate 142: All-cause AEs and treatment-related AEs (adapted from CS, Table 18) ERG states that AEs leading to discontinuation were ▮▮% any grade AEs and ▮▮% grade 3-4 AEs, however, these represent treatment-related AEs.	It should be specified in this table that these are percentages for treatment-related AEs that lead to discontinuation.	As described in B.2.10.1.6 in the CS "All causality AEs leading to discontinuation were reported in ▮▮ of patients (any-grade), and ▮▮ of patients (Grade 3–4). TRAEs leading to discontinuation were reported at a frequency of ▮▮ (any grade) and ▮▮ (Grade 3–4)."	Not a factual inaccuracy. The table provides data on both all-cause and treatment-related AEs leading to discontinuation, any grade AEs and serious AEs.
P85 Section 3.5.1 The ERG states: "Patients in CheckMate 142 continued nivolumab therapy until disease progression or unacceptable toxicity, whereas the draft Summary of Product Characteristics (SmPC) recommends that nivolumab therapy is continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. This means that treatment may be continued beyond progression if a patient is deemed to still derive a clinical benefit or discontinued prior to progression in patients with limited clinical benefit."	The current ERG report statement is misleading. The CheckMate 142 dosing schedule reflects the SmPC and use of the word "whereas" implied conflicting dosing schedules. Hence, this should be updated to reflect concordance.	CheckMate 142 is aligned to the SmPC. As noted in the ERG report, ▮ patients received nivolumab therapy post-progression. Further, of the ▮ patients who discontinue treatment, ▮ discontinued due to disease progression, ▮ discontinued due to adverse events (related or unrelated to study drug) and ▮ discontinued due to patient request. Additionally, ▮ discontinued due to maximum clinical benefit. Hence, CheckMate 142 reflects the SmPC and the ERG statement can be considered misleading.	Not a factual inaccuracy. No change required.

Issue 3   MAIC

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
p.72 Section 3.4.3 MAIC methods The ERG states that the "log mean difference" is taken as the relative treatment effect.	This should be amended to the difference in log mean	"Log mean difference" implies that the logarithm of the mean of a number of differences has been taken. This is not correct. The correct measure is as in the bullet point above – the difference in the logarithm of the mean survivals, which may also be referred to as the logarithm of the ratio of the mean survivals.	The ERG thanks the company for highlighting this error. The report has been amended.

Issue 4   Survival analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
p.22 Section 1.3 Summary of ERG's key issues, and p. 104 Section 4.2.6.1.4 ERG critique The ERG is considerate of *when* the treatment effect of NIVO+IPI develops, but not the form it takes.	The ERG should modify their preferred case such that a decreasing excess hazard model is used.	The ERG did comment that the treatment effect for PFS may start earlier than the company's preferred base case, which is a matter of opinion that influences not only the location of the parametric portion of the hazard profile, but also its shape. They also stated that the hazard does not approach constancy until month 10. Therefore, applying a constant hazard model including the data over the period 2.99 – 10 months is overestimating the mean hazard beyond 10 months within the observed data and potentially into extrapolation. The conservatism of the company base case should be respected in maintaining constant hazard from 6.44 months onwards, and if the cut-point is to be moved further back into the higher hazard region of data, then the parametric portion of the model must be allowed a decreasing hazard to compensate for this.	This is not a factual inaccuracy. No change required.
p. 26 Section 1.3 Summary of ERG's key issues, and p. 118 Section 4.2.7	Paragraphs requesting the use of an excess mortality model should be removed.	The "relative survival" models fitted by the company comply exactly with the specification of an "excess mortality" model. For clarification, an "excess mortality" model consists of the modelling of an	This is not a factual inaccuracy. As noted in the ERG report, the company has not disentangled ACM

Mortality The ERG has misunderstood the compatibility of a relative survival and excess mortality model.		event as the result of two differing hazards. If these hazards are independent, then the total hazard h_t is the sum of the baseline hazard h_b (e.g. from lifetables) and the excess hazard h_e (due to disease). $h(t) = h\_b(t) + h\_e(t)$ The survival function that results from the integration of this hazard over time is equivalent to the multiplication of the survival curves derived from integration of the baseline and excess hazard functions independently. $S(t) = S\_b(t) * S\_e(t)$	from the extrapolated CheckMate 142 survival curves. As such, the company has not used an "excess survival" model as described in NICE DSU TSD 21.
p. 96 Section 4.2.5.1 ERG critique The ERG states that there is "the phenomenon that the probability of survival is higher for patients with the disease than the general population from year 32".	This paragraph should be deleted.	The paragraph is based upon omission of ACM from the model. The survival models used are relative survival (excess mortality) models, and so the component being modelled after removal of the general population ACM component is only the disease-specific survival. It is therefore incorrect to state that "the probability of survival is higher" in this scenario, because not all causes of death have been accounted for.	This is not a factual inaccuracy. No change required. The previous sentence clearly states that the phenomenon is when "ACM is omitted from the model"
p.112 Section 4.2.6.2 Comparators, p. 112, Table 28 Summary of PFS MAIC comparator data RECOURSE/USA is described as being a scenario analysis of 30 study sites in China, the Republic of Korea and Thailand.	The Scenario text should be amended to '21 study sites in the USA'.	The RECOURSE/USA subgroup analysis is based upon the USA regional subgroup of RECOURSE, as reported in van Cutsem "The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer" [1].	The ERG thanks the company for highlighting this error. The report has been amended.

Issue 5   Cost-effectiveness modelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
p. 95-96 Section 4.2.4.1 ERG critique of the modelling approach and model structure The ERG state: *"For these reasons, the ERG considers that an alternative model structure should have been considered by the company; that is, a state transition model where PPS is explicitly modelled, and OS depends on the time spent in PFS and PPS. During the clarification stage, the company was asked to consider this alternative. In their response the company explained that survival data from CheckMate 142 is sufficiently mature to conclude that outcomes are significantly improved versus comparators. The company also highlighted that PPS outcomes are not available from the comparator studies and that a large amount of time would be needed to undertake the analysis."* This does not fully reflect the rationale why this is not feasible. In particular, the company highlighted that it would add uncertainty in terms of attempting to assign pre- and post-progression mortality. Further, it would require significant assumptions that may or may not be appropriate for different	This suggestion should be retracted as it would provide additional uncertainty. Alternatively, further company rationale should be reflected	Constructing a state transition model has inherent limitations, including: • As outlined in Figure 69 of the CS, there are very few pre-progression death events during CheckMate 142. Extrapolation of this data may produce spurious results and increase the uncertainty, especially for MAIC results. • PPS for comparators is not available from comparator studies, which most commonly report PFS. As PFS definitions include deaths as an event, use of this data to inform a state transition model will result in double counting, biasing against comparators and increasing uncertainty. • PPS is not equivalent to the difference between OS and PFS. PPS is properly defined as the time from progression to death, whereas both OS and PFS are defined from baseline.	The ERG thanks the company for highlighting this issue. The ERG report has been amended.

comparators		As no patients are at risk in the post-progression state at baseline, the hazard of death from post progression as a function of time from baseline is not described by a survival function.	
p. 96 Section 4.2.5.1 ERG critique of the perspective, time horizon and discounting The ERG state: *"The ERG also notes that the time horizon could be shortened from 50 years to 45 years as this is the time all-cause mortality (ACM) caps OS to 0% survival."*	This suggestion would not be valid when conducting a PSA, which provides variation on the baseline age of the modelled cohort.	Whilst the company acknowledges that a time horizon of 45 years would be sufficient for the base case deterministic analysis, where a mean age of 56.6 years is applied, this may not be sufficient to fully capture the entire costs and benefits of patients whilst conducting a PSA, where the age may vary around the mean value using a standard error. A time horizon of 50 was used to allow for any variations in the mean age that may be a result of probabilistic sampling.	The ERG thanks the company for highlighting this issue. The ERG report has been amended.
p. 123 Section 4.2.9 ERG critique of health-related quality of life ERG state: "*Furthermore, the ERG cannot identify the HSUVs used by the company in the CORRECT publication[1]. The pre-progression HSUV is similar (0.75 vs 0.74), but there is a large discrepancy in the post-progression HSUV (0.59 vs 0.69).*"	The base case analysis for the company submission uses health-state utilities sourced from TA242[2] to inform off treatment utility (assumed to be equal to post-progression utility), as well as the pre-progression and post-progression utilities for comparator arms.	Whilst the company acknowledges that Table 34 on the CS does state the source of the utilities are from the CORRECT[3], it is in fact stated in Table 22 of the CS that utility values are supplemented with utility values from TA242[2].	The ERG thanks the company for explaining this discrepancy. The ERG report has been amended. However, in the company's response to technical engagement, the ERG would like the company to explain why TA242 was preferred over TA405.
P111 Section 4.6.1.4 ERG critique The ERG notes that TA439 concluded that it	The sentence around TA439 should be amended to reflect that	TA439 described use of EGFR inhibitors (cetuximab and	This is not a factual inaccuracy and therefore no changes to

was inappropriate to implement a stopping rule in people with mCRC. This TA reflects a drug with a different mechanism of action and this assumption may be less appropriate with immuno-oncology agents due to the differences in mechanism of action and evidence base.	cetuximab and panitumumab are EGFR inhibitors and evidence is less supportive of long-term efficacy, particularly when using a stopping rule.	panitumumab), which is a completely different mechanism of action to nivolumab and ipilimumab. Across indications, there is significant evidence supporting stopping rules for immunotherapies in patients demonstrating clinical benefit. Hence, the conclusion may be less appropriate for this TA. This uncertainty should be acknowledged.	the report are required.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG comment
p. 60 Section 3.3.3 Safety "The most common AESIs by category were skin (▇▇%), gastrointestinal (▇▇%), and hepatic (▇▇%)".	This is unpublished data from CheckMate 142 and should be marked as AIC.	Mark results as AIC as follows: The most common AESIs by category were skin (▇▇%), gastrointestinal (▇▇%), and hepatic (▇▇%).	The ERG thanks the company for highlighting this error. The ERG report has been amended to include the AIC marking.

References

1.   Van Cutsem E, Mayer RJ, Laurent S, Winkler R, Grávalos C, Benavides M, et al. The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer. Eur J Cancer. 2018;90:63-72.

2.   National institute for Health and Care Excellence. Technology appraisal guidance [TA242]: Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for

the treatment of metastatic colorectal cancer after first-line chemotherapy 2012 [Available from: https://www.nice.org.uk/guidance/ta242.

3.	Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet (London, England). 2013;381(9863):303-12.

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As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm, 16 March 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under ███████████████████████, all information submitted under ████████████████████, and all information submitted under ███████████ in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the [Guide to the processes of technology appraisal](#) (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Sarah Kassahun**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bristol-Myers Squibb Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

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Executive summary

Ahead of addressing the key issues presented in the Technical Engagement response, there are two updates to the available data to be presented:

1. Updated database lock from CheckMate 142 (███████)

2. Updated agreed PAS for nivolumab of ███.

For clarity, all results and argumentation presented in this response apply this updated database lock and PAS. Hence, the impact of these updates is briefly described below and in appendices.

Updated database lock from CheckMate 142 (██████)

As previously discussed, outcomes from an updated database lock from CheckMate 142 (████████) have become available. These data support sustained benefits for nivolumab plus ipilimumab (NIVO+IPI) during CheckMate 142 , with OS and PFS Kaplan-Meier exceeding outputs from the previous database lock. Of note, the updated database lock reflects the updated protocol, wherein patients who had achieved maximal clinical benefit were able to cease treatment. At database lock, ████ of patients had discontinued treatment, for a median time on treatment of ███ months.

Data from the updated database lock are presented in the updated survival analysis (Appendix 1), updated utility analysis (Appendix 2) and updated MAIC analysis (Appendix 3). Based on the analysis with the updated database lock, survival was extended while utility and ITC analyses yielded similar conclusions compared with previous database lock analysis.

Updated agreed PAS for nivolumab

The agreed PAS for nivolumab has been updated from ██ to ███, impacting on vial costs as follows:

- 4ml vial: 439.00 (with PAS: ██████)

- 10ml vial: £1,097.00 (with PAS: ██████)

- 24ml vial: £2,633.00 (with PAS: ██████)

This updated PAS has been applied within this response. For reference, previous base case analyses including this PAS are provided in Table 1 alongside the company's preferred base case post-technical engagement. Please note that the preferred case post-technical engagement includes data from the ███████DBL, the updated PAS, removing the stopping rule amongst other changes. A full set of updates to the base case are listed in Table 1 of Appendix 4.

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Table 1. Cost-effectiveness results

	Company submission (NICE submission pre-technical engagement February 2019 DBL with updated PAS)	Post TE base case (███████████, updated PAS and updated model assumptions)
FOLFOX	£14,053	£17,220
FOLFIRI	£14,145	£17,981
Trifluridine-tipiracil	£12,615	£15,743
BSC	£13,483	£16,323

As outlined in company submission, NIVO+IPI provides an opportunity to make a significant and substantial impact on health-related benefits and address a current unmet need in the management of MSI-H mCRC. The outcomes of the additional database lock surpass the previously reported data and further support the beneficial impact of NIVO-IPI on the management of this life-threatening condition.

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Indirect treatment comparison Is the partially adjusted matching-adjusted indirect comparison (company preference) or naïve indirect treatment comparison (ERG preference) more relevant for decision making?	**Yes** - The ITC analysis has been updated using the CheckMate 142 ▇▇▇▇▇ database lock (DBL), described in Appendix 3. This database lock provides an additional 18 months' worth of follow up to inform the MAIC. Further CE analyses use the updated nivolumab PAS,	**The company believes that the partially adjusted MAIC analysis is the more relevant analysis for decision making. However, it should be noted that several supporting analyses (naïve ITC, fully adjusted MAIC), have been presented and are supportive of conclusions for both relative clinical effectiveness and cost-effectiveness.** Updated MAIC analyses are presented in Appendix 3 and the company has presented both a partially adjusted (company base-case) and a naïve (scenario) indirect comparison. Appendix 4 contains updated cost-effectiveness analyses applying the updated nivolumab PAS. **Rationale for use of the partially adjusted MAIC over naïve ITC** The partially-adjusted MAIC compensates for many of the observed outcomes-modifying population differences identified in CheckMate 142. The direction of adjustment is generally plausible, e.g. increasing number and prevalence of metastatic sites tends to worsen prognosis. Therefore it is credible that bias is being reduced in forming the comparison in the comparator trial population. CheckMate 142 is insufficiently sized to allow for compensation of all differences, and some subgroups have very low prevalence in the CheckMate population,

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	detailed in Appendix 4.	resulting in poor sampling of outcomes. In a large enough ensemble, noise due to this poor sampling would be removed, but with a single instance of a small trial, the only statistical solution is to use methods that generate highly conservative confidence intervals. To discard data where bias is reduced due to the inability to exactly match on all prognostics would not be an appropriate approach. Expert opinion gives credible margins for the expected efficacy of comparators in the MSI-H population, even without direct measurement, and the behaviour of the partial adjustment can be reasonably assessed. Hence, the population of CheckMate 142 and the reliability of the outcomes thus derived can be similarly scrutinised.

The ERG report comments on a potential bias resulting from the MAIC analysis. The company believes that any bias resulting from the MAIC analysis is in favour of the comparator treatments. The reason for this is the lack of published literature in the MSI-H mCRC population, which required a comparison of CheckMate 142 trial outcomes for NIVO+IPI in MSI-H patients to evidence for chemotherapies used within the overall mCRC patient population. As described in the company submission, recent evidence indicates that MSI-H patients have worse prognosis and outcomes in terms of survival compared with the overall mCRC population. This was further validated by clinicians consulted in association with this submission. Therefore, it is likely that the efficacy identified for comparator treatments is an overestimation of the treatment efficacy expected for patients with MSI-H mCRC.

Rationale for exclusion of fully adjusted set
Informing the extrapolative survival models used to predict mean survival requires a distribution of events over time, and in discussion with the ERG, it was agreed that a very low minimum scaled number of events (5) would be used as a threshold, below which fitting on the fully adjusted sets would not be attempted. The fully adjusted sets (using all available covariates) resulted in ESS < 5 and therefore were not considered to be accurate enough to include in the analysis. |

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Impact of different ITC scenarios

The ICERs as a result of the updated MAIC (keeping all other parameters as the base-case) are presented in Table 2 below. As with the previous DBL, the cost-effectiveness results remain robust to alternative analysis methods and source of comparator data (see Appendix 3 for more details). Hence, although there is uncertainty about specific survival estimates for the comparators, there is no uncertainty around the magnitude of clinical effectiveness benefit for NIVO+IPI and the cost-effectiveness conclusions can be considered relatively stable.

Table 2. Impact of alternative comparator outcomes

Comparator outcomes	Trifluridine-tipiracil	BSC	FOLFOX	FOLFIRI
Feb 2019 DBL; partially adjusted	£12,615	£13,483	£14,053	£14,145
Feb 2019 DBL; unadjusted (naïve)	£12,556	£13,452	£14,257	£14,204
▉▉▉ DBL; partially adjusted	£15,743	£16,323	£17,220	£17,981
▉▉▉ DBL; unadjusted (naïve)	£15,555	£16,231	£17,127	£17,098

NB: this does not reflect the final revised base case analysis, as additional assumptions are also updated. The final revised base case analysis is presented in the executive summary and Appendix 4.

Key issue 2: Stopping rule	Yes - The	
Does the company preference (2-year stopping rule) or ERG preference (no stopping rule) best reflect how nivolumab plus ipilimumab would be used in clinical practice?	analysis has been updated using the CheckMate 142 ▉▉▉ database lock (DBL), described	**Additional analyses are presented without the two-year stopping rule applied in the economic model, but where time on treatment data reflects an optional stopping rule introduced into CheckMate 142 in February 2019.** The reason the company included the 2-year stopping rule applied in the economic model in the original submission was:

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	in Appendix 1. Further CE analyses use the updated nivolumab PAS, detailed in Appendix 4.	I. to reflect the expected treatment duration in UK clinical practice, as outlined by UK clinical experts and as evidenced by patients in other disease areas, who are consistently treated with nivolumab for a maximum of 2 years.[1,2] II. to reflect the maximum clinical benefit optional stopping rule that was introduced into the CheckMate 142 trial protocol in February 2019, through which investigators were able to discontinue ongoing treatment with nivolumab if they felt that the patient had achieved maximum clinical benefit. This is supported by forthcoming evidence from the CheckMate 8HW study, where this stopping rule has been applied. Given this protocol amendment was implemented only shortly before the February 2019 DBL, only ▮ patients had stopped treatment due to maximum clinical benefit at the time. However, in the ▮▮▮▮▮ DBL, the impact of this protocol amendment is better captured due to more mature time on treatment (ToT) data from this lock. This reduces uncertainty around treatment duration in the model. In addition, given the absence of a formal stopping rule in the trial, this provides an estimate for time-on-treatment for patients under real-world practice. Figure 1 and *Figure 2 present the time on treatment curves for the February 2019 and the ▮▮▮▮▮ DBL, respectively. Updated cost-effectiveness results applying the most recent DBL are presented in Appendix 4. For reference the company's preferred base case ICERs (which includes removing the stopping rule and time on treatment model fitted as per company submission) are now £15,743, £16,323, £17,220, and £17,981 versus Trifluridine-tipiracil, BSC, FOLFOX, and FOLFIRI respectively. *Figure 1. CheckMate 142: Time on treatment; February 2019 DBL* ▮*Figure 2. CheckMate 142: Time on treatment; ▮▮▮▮▮ DBL* ▮

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Key issue 3: Survival extrapolations	**Yes -** The analysis has been	**The company prefer use of the semi-parametric model using KM curve to**
Which survival extrapolations are most appropriate for decision making? • Company: Semi-parametric model using KM curve to 6.44 months • ERG: Semi-parametric model using KM curve to 2.99 months	updated using the CheckMate 142 ▮▮▮▮▮ database lock (DBL), described in Appendix 1. Further CE analyses use the updated nivolumab PAS, detailed in Appendix 4.	**6.44 months, particularly for the updated database lock. However, it should be noted that both approaches provide similar outcomes, do not impact greatly on clinical effectiveness outcomes and do not change cost-effectiveness conclusions.** **Rationale for use of 6.44 month cut point over 2.99 month cut point** As part of the submission, multiple methods of survival modelling were explored. As noted in the response to the ERG clarification questions, survival outcomes were comparable between extrapolation methods and cost-effectiveness conclusions were relatively insensitive to changes in modelling methods. This consistency has carried over to the updated database lock where both the 6.44 month and 2.99 month cut points have been assessed, as provided in Appendix 1. The company believe that the semi-parametric model using KM curve to 6.44 months is the most appropriate and uses this in their base-case analysis. The extended follow-up from CheckMate 142 supports this, as the long-term marginal hazard of PFS continues to decline, indicating further against including the influence of the early, high-hazard period in extrapolation. For PFS, the point at which the hazard profile approached a constant excess was at earliest 6.44 months. Further inspection of the cumulative hazard gradient (Figure 3, Figure 4) revealed that the period between 2.99 months and 6.44 months experienced a higher gradient than the average for the remainder of the profile (indicated by red square on Figure 3), indicating that the longer-term hazard profile was still developing and its inclusion in a constant excess hazard would be inappropriate. The ERG report states: "based on feedback from the ERG's clinical experts and visual inspection of the KM curves, cumulative hazard plots and diagnostic plots, the effect of NIVO+IPI starts to become apparent at around 3 months rather than after 6 months". The ERG report further states that the key reason for choosing these models is because they represent the initial high hazard well and extend the amount of data that can be used to inform the long-term extrapolation. However,

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as outlined in Appendix M, these models reflect an evolving hazard profile and do not well represent outcomes observed in the ████████ database lock. Further, with longer-term data available, there is limited rationale to using an earlier cut point to conserve data when the hazard profile continues to evolve.

Figure 3. CheckMate 142: Cumulative hazard, PFS per investigator from 2.99 months; ██████ DBL (red square indicates period of evolving hazard)

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Figure 4. CheckMate 142: Cumulative hazard, PFS per investigator from 6.44 months; ██████████

█

Impact of alternative survival modelling approaches on survival outcomes
At the ERG clarification stage, based on the Feb 2019 DBL, the company explored multiple approaches to survival extrapolations and demonstrated that the ICERs remained stable (see ERG clarification question B5 and Table 9 of ERG report). Survival outcomes from the updated ████████ DBL demonstrated more of a plateau and suggested increased survival versus the predicted survival in the company base case analysis, suggesting that the semi parametric approach is likely conservative in estimating the long-term benefit of nivolumab plus ipilimumab.

Impact of alternative cut points on cost-effectiveness outcomes
Probabilistic analyses were run using models fitted to the updated DBL and demonstrated decreased uncertainty in the economic outcomes. The probability of cost-effectiveness versus trifluridine-tipiracil, BSC, FOLFOX and FOLFIRI was predicted to be ██, ██, ██ and ██, respectively. Table 5 to Table 8 in Appendix 4 presents the impact of alternative cut points and extrapolations on the cost-effectiveness. Plausible ICERs ranged from £14,354 to £18,778 per QALY, providing evidence of a robust estimate of cost-effectiveness in the base case (NB: this does not reflect the final revised base case analysis, as additional

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		assumptions are also updated. The final revised base case analysis is presented in the executive summary and Appendix 4.). Hence, although there are alternative survival modelling approaches that could be used, there is very little uncertainty around the magnitude of clinical effectiveness benefit for NIVO+IPI and the cost-effectiveness conclusions can be considered relatively stable.
Key issue 4: Progression-based utility values Which source of utility values is most appropriate for progression-based utilities? • Company: Taken from TA242. Pre-progression utility of 0.75; Post-progression utility of 0.69 • ERG: Taken from CORRECT publication. Pre-progression utility of 0.74; Post-progression utility of 0.59	**Yes -** CE analyses use the updated nivolumab PAS, detailed in Appendix 4.	**The company believe that progression-based utilities from TA242 are more appropriate than those from CORRECT (in the absence of treatment specific utilities).** The CORRECT[3] trial and the study used in TA242[4] reflect different placements in the treatment pathway.TA242 reflects patients who have previously received first-line treatment. By contrast, CORRECT enrolled patients who had received available standard therapies, with nearly half of patients in CORRECT (49% in the regorafenib arm and 47% in the BSC arm) having received at least four systemic anticancer therapies for metastatic disease. The NIVO+IPI arm of CheckMate 142 is more representative of the TA242 population than the CORRECT patient group, as 23% of patients had received only one prior therapy and 36% had received only two prior therapies. Hence, post-progression utilities are better aligned to the TA242 values, than they are the CORRECT utility values. However, the impact of applying CORRECT utility values in the ▮▮▮▮▮ DBL has been assessed and results are presented in Table 3. As can be seen, although the ICERs increased versus the base case, the cost-effectiveness of NIVO+IPI remains below the £50,000 per QALY threshold. Detailed results can be found in Section 1.2.3.4 in Appendix 4.

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		Table 3. Impact of alternative utility assumptions			
		Assumption	**Trifluridine-tipiracil**	**BSC**	**FOLFOX**	**FOLFIRI**
		Progression-based TA242 utilities	£15,548	£16,127	£16,996	£17,738
		Progression-based CORRECT utilities	£16,639	£17,248	£18,104	£18,957
		NB: this does not reflect the final revised base case analysis, as additional assumptions are also updated. The final revised base case analysis is presented in the executive summary and Appendix 4.				

Key issue 5: Utility approach Which utility approach is most appropriate? • Company: Utilities according to treatment status for nivolumab plus ipilimumab, and progression status for the comparators • ERG: Utilities according to progression status for all treatments, using the values from CORRECT	**Yes -** The analysis has been updated using the CheckMate 142 ▉▉▉▉ database lock (DBL), described in Appendix 2. Further, CE analyses use the updated nivolumab PAS, detailed in Appendix 4.	**The company believe that treatment specific utilities for NIVO+IPI are appropriate given the significant survival benefit seen with NIVO+IPI vs standard of care, which will translate to higher quality of life for these patients.** **Outcomes in the updated database lock** **Utility analysis using the extended CheckMate 142 DBL from ▉▉▉▉ was conducted and the utility value for patients receiving NIVO+IPI was ▉▉, marginally ▉▉ than in the company submission (▉▉) .** This on-treatment utility value for NIVO+IPI of ▉▉ was also higher than the general population matched utility value. This indicates that patients undergoing treatment with NIVO+IPI demonstrate ▉▉▉ QoL versus their pre-treatment period, and across the measured domains of the EQ-5D-3L instrument are ▉▉▉▉▉▉ by utility from an age and sex matched general population English cohort when the same tariff is applied. The company accepts that utility values higher than the general population utility value are not expected. For face validity, utility values applied in the base case analysis have been limited to that of the general population. Clinical understanding indicates that immunotherapies can return quality of life to patients, particularly versus highly toxic chemotherapy used as standard of care, and allow a portion of

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patients to enter a state of long-term remission. Hence, a utility value similar to the general population is not implausible.

Table 4. Impact of updated database lock on utility values

	Utility value outputs	Economic model input
February 2019 DBL	███	███
████████	███	███

Rationale for treatment-specific utilities

Clinicians consulted during the appraisal process confirmed that utility values can be expected to be different between NIVO+IPI and the comparators, not simply based on the novel mechanism of action, but also due to the improved survival benefit and the reduced chemotherapy toxicities. This cannot be captured by simple health state utilities, as patients on treatment who have recently responded and are progression-free will have different quality of life to patients who have completed treatment having achieved maximal clinical benefit and remain progression-free at five years.

The ERG report notes three key clinical expert concerns regarding treatment-specific utilities, as noted in Table 5.

Table 5. ERG clinical expert opinion

ERG expert opinion	Rationale
They would not expect a meaningful difference in the HSUVs between treatments and concluded that a novel mechanism of action alone was insufficient to warrant	It should be noted that mechanism of action alone is not the rationale for treatment-specific utility values. Patients will have recently completed a regimen including highly toxic chemotherapy (e.g. FOLFIRI or FOLFOX with or without a biologic treatment). Patients receiving NIVO+IPI report greatly improved quality of life, potentially due to the comparison with the highly toxic combination regimen that they may have received.

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		treatment-specific utility values	Further, quality of life improvements associated with NIVO+IPI cannot be captured by simple health state utilities. Patients on treatment who have recently responded and are progression-free will have different quality of life to patients who have completed treatment having achieved maximal clinical benefit and remain progression-free at five years. Additionally, patients receiving NIVO+IPI have significantly longer OS and longer PFS than patients receiving standard of care. Time to progression or death is a key driver in deterioration in quality of life, as evidence by several prior NICE appraisals. Hence, it is more accurate to say that the novel mechanism of action for NIVO+IPI drives several key benefits, including improved toxicity and survival, that cause improved quality of life.
		They would expect someone receiving second line treatment for mCRC to have a lower QoL than the general population (some patients may value their life very highly because they are thankful to be alive, but this would be overridden with the consequences of mCRC)	It is acknowledged that this is generally the case for patients with mCRC, where survival is likely to be short and outcomes poor. However, outcomes from CheckMate 142 indicate that NIVO+IPI is associated with outcomes unlike any prior therapy, providing significant promise of long-term remission, which would be associated with QoL equivalent to the general population.
		They would expect the toxicities associated with IPI to have a large negative impact on patients' QoL.	Outcomes from CheckMate 142 do not indicate a large safety impact associated with IPI. The dosage of ipilimumab is also 4 doses at 1mg/kg, which is lower than has previously been seen in other indications and considered more tolerable. However, if this were the case, there is no evidence to indicate that it would be more toxic than complex regimens such as FOLFOX and FOLFIRI.

Therefore, the company believes that the most appropriate base case analysis uses treatment-specific utilities for the pre-progression state; in the absence of

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data, post-progression utilities are assumed to be the same as standard of care. However, given the uncertainty stated in the ERG report, the company has run a number of scenario analyses as part of the technical engagement response. Scenarios based on progression status are provided in Table 6 below.

In addition, the scenario suggested by the ERG on page 123 of the ERG report (lower week 7 utility for NIVO+IPI of 0.767 for the first 7 weeks of treatment), has been provided to account for the disutility associate with IPI. However, it should be noted that ipilimumab is provided at a lower, more tolerable dose, in this combination (1mg). The impact of exploring alternative scenarios assessing the impact of a lower utility for the first 7 weeks of treatment with NIVO+IPI, the on treatment, progression-based utilities and a combination of the two are presented in Table 6. As can be seen, the ICERs were increased versus the base case, however all cost-effectiveness conclusions remain the same.

Table 6. Impact of alternative NIVO+IPI utility assumptions

Assumption	Trifluridine-tipiracil	BSC	FOLFOX	FOLFIRI
Lower utility for the first 7 weeks	£15,769	£16,349	£17,250	£18,014
On treatment, progression-based utilities	£15,877	£16,457	£17,374	£18,148
Combination of the above	£15,899	£16,480	£17,400	£18,176

NB: this does not reflect the final revised base case analysis, as additional assumptions are also updated. The final revised base case analysis is presented in the executive summary and Appendix 4.

As presented above the utility values used in the model have been robustly tested, and NIVO+IPI remains a cost-effective treatment option.

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Key issue 6: Subsequent treatment Do the subsequent treatment scenarios explored by the company (a one-off cost derived from TA405 for all treatment arms, and a weekly cost calculated from this one-off cost) reflect subsequent treatments in clinical practice?	**Yes -** The analysis has been updated using the CheckMate 142 ██████ database lock (DBL). Further, CE analyses use the updated nivolumab PAS, detailed in Appendix 4.	**The subsequent treatment scenarios explored by the company represent the best available evidence for subsequent treatment in clinical practice. In the revised base case analysis, the subsequent treatment cost has been updated to be slightly higher in the NIVO+IPI arm. Additional scenarios have been run at the request of the ERG.** **Rationale for updated base case analysis input** In the company submission, the same one-off subsequent treatment cost was applied to all treatment arms as it was not expected that there would be a significant difference in treatment type post progression (third line and beyond) between the arms. In addition on page 155 of the ERG report, the ERG accept the assumption of applying a one off cost. **Clinical expert advice elicitation** In the ERG report, the ERG also recommended to use the SHELF methodology to obtain aggregate judgements on the subsequent treatment regimens with which patients are likely to be treated upon NIVO+IPI discontinuation. The company reviewed this approach and after careful consideration it was concluded that this approach would not be feasible given the limited time that was available to conduct this. Instead, unstructured interviews with clinicians were conducted in order to obtain the most detailed insight possible during the technical engagement process. The company consulted 4 clinicians from across the UK to gain more information on the composition and duration of subsequent treatments following NIVO+IPI and the relevant comparators (FOLFOX, FOLFIRI, Trifluridine-tipiracil, BSC). A detailed

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overview of the responses can be found in Appendix 5. In brief, clinicians reported the following:

- Patients who have received NIVO+IPI may be considered for FOLFOX or FOLFIRI, whichever they had not received in first-line

- A proportion of patients who received NIVO+IPI or comparators would have BRAF mutations (approximately one third of the MSI-high patients) and these patients would be eligible for treatment with encorafenib plus cetuximab which has recently been approved by NICE.[5]

- Trifluridine-tipiracil is the only NICE funded option following second-line treatment, which would be followed by best supportive care (BSC)

  - Due to its limited benefit and toxicity, clinicians would try to access IO therapies through clinical trials instead of treatment with trifluridine-tipiracil

- Regorafenib has a license and can be used third-line or fourth-line through self-funding, however, it has high toxicity.

- Treatment from third-line is more nuanced and patients can be offered experimental options

In order to assess the impact of subsequent treatments provided by clinical expert opinion, a weighted one-off costs were calculated using treatment pathways suggested by the clinician along with costs, dosing schedules and the time patients received treatment sourced from literature using the most relevant sources. The full derivation of these costs is provided in Appendix 4. As in the base case, a one-off cost was applied to patients in the cycle of discontinuation for both treatment

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arms. Table 7 provides the results on the scenario analysis and as can been, all ICERs remain below the £50,000 per QALY threshold.

Table 7. Impact of subsequent treatments based on clinical expert opinion

Assumption	Trifluridine-tipiracil	BSC	FOLFOX	FOLFIRI
Subsequent treatments based on clinical opinion	£16,644	£17,198	£17,520	£18,214
Subsequent treatments including encorafenib + cetuximab for BRAF mutated patients	£18,085	£18,595	£17,780	£18,332

NB: this does not reflect the final revised base case analysis, as additional assumptions are also updated. The final revised base case analysis is presented in the executive summary and Appendix 4.

Alternative methods of deriving subsequent treatment costs
In addition, analysis of subsequent treatment (subsequent treatments received by more than one patient only) in the CheckMate 142 ███████ DBL has been conducted. Patients who discontinued in a cycle incurred the full cost of subsequent treatments, which was accrued as a one-off cost. As in the scenarios based on clinician validation, costs and dosing schedules were sourced from the most relevant data sources. CheckMate 142 was unable to supply sufficient data to inform the duration of time patients were in receipt of these subsequent treatments and therefore data from the literature was used to supplement the analysis. The full derivation of these costs is provided in Appendix 4. Table 8 presents the impact of these scenario analyses and as can be seen, all ICERs remain below the £50,000 per QALY threshold.

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Table 8. Impact of subsequent treatments from CheckMate 142

Assumption	Trifluridine-tipiracil	BSC	FOLFOX	FOLFIRI
Subsequent treatments from CheckMate 142	£15,837	£19,088	£17,549	£18,131

NB: this does not reflect the final revised base case analysis, as additional assumptions are also updated. The final revised base case analysis is presented in the executive summary and Appendix 4.

Key issue 7: Adjustment for all-cause mortality Is the way in which the company have adjusted for all-cause mortality appropriate?	**Yes -** The analysis has been updated using the CheckMate 142 ▮▮▮▮▮ database lock (DBL), described in Appendix 2.	**The company base case has been updated to reflect relative survival across the entirely of the model time horizon.** The approach in the company submission reflected Kaplan-Meier data to 6.44 months (with no added ACM), followed by ACM-adjusted extrapolated curves. The approach taken in the company submission was in line with TSD21. However, in the Technical Engagement clarification call, it was understood that it is the ERG's preference for the full survival model to be evaluated as a relative survival model, inclusive of the initial, Kaplan-Meier section. By removing the trial matched lifetable hazard from these sections, both pieces of the piecewise models of PFS, OS and TOT for NIVO-IPI were made relative survival, and the matched scenario baseline hazard profile was then applied in the economic model over the full time horizon.

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Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Relative utility in progressed disease between on and off treatment	**4.2.9 pp 122**	**No**	The labels applied in the source table for the on and off treatment subgroups of the progressed disease dataset were ambiguous and have been reversed. The correct table is reproduced as part of the appended utility analysis (Appendix 2). In this table, it is revealed that the on-treatment dataset consists of the majority of post-progression observations, and, as expected the on-treatment post-progression utility is higher than the mean post-progression utility.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Summary of revised base case analysis (additional detail provided in Appendix 4)			
Base case	**Incremental QALYs**	**Incremental Costs**	**ICER (cost/QALY)**
Company's preferred base case following technical engagement	Trifluridine-tipiracil: ▓▓▓ BSC: ▓▓ FOLFOX: ▓▓▓ FOLFIRI: ▓▓	Trifluridine-tipiracil: ▓▓▓ BSC: ▓▓▓ FOLFOX: ▓▓▓ FOLFIRI: ▓▓▓	Trifluridine-tipiracil: £15,743 BSC: £16,323 FOLFOX: £17,220 FOLFIRI: £17,981
Impact of individual updates to the base case in response to the key issues (NB: ICERs provided below reflect the impact of individual changes and do not reflect the final revised base case analysis)			
Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Issue 1: comparator outcomes	The company base case applied a MAIC analysis to estimate the comparator outcomes.	The company prefers to use the partially adjusted MAIC analysis, and have updated results using the ▓▓▓▓ DBL of CheckMate 142.	Updated ICERs using the partially adjusted MAIC using the ▓▓▓▓ DBL of CheckMate 142 (full details of model settings

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			are provided in Appendix 4) Trifluridine-tipiracil: £12,737 BSC: £13,536 FOLFOX: £14,341 FOLFIRI: £15,128
Issue 2: stopping rule	The company base case applied a 2-year stopping rule. All patients who were receiving NIVO+IPI at 2 years ceased treatment and received no further costs associated with NIVO+IPI.	The updated ███████ DBL provides a more mature time on treatment curve, which accounts for the maximum clinical benefit associated with NVO+IPI from the trial. The company therefore removes the 2-year stopping rule from the economic model and patients remain on treatment in line with the time on treatment curve.	Updated ICERs removing the stopping rule and using the ███████ DBL of CheckMate 142 (full details of model settings are provided in Appendix 4) Trifluridine-tipiracil: £18,403 BSC: £19,074 FOLFOX: £20,069

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			FOLFIRI: £20,150
Issue 3: survival extrapolations	The company base case used extrapolated survival curves based off patient-level data from the February 2019 DBL.	The updated ▮▮▮▮▮ DBL was used to inform survival extrapolations in the model.	Updated ICERs using survival data from the ▮▮▮▮▮ DBL of CheckMate 142 (full details of model settings are provided in Appendix 4) Trifluridine-tipiracil: £10,673 BSC: £11,466 FOLFOX: £11,812 FOLFIRI: £11,893
Issue 5: treatment-specific utilities	The company base case applied the utility from CheckMate 142 for patients whilst they remained on NIVO+IPI.	The company base case keeps the same assumption, however uses an updated utility value based on the ▮▮▮▮▮ DBL	Updated ICERs using updated utility data from the ▮▮▮▮▮ DBL of CheckMate 142 (full details of model settings are provided in Appendix 4)

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			Trifluridine-tipiracil: £12,595 BSC: £13,462 FOLFOX: £14,030 FOLFIRI: £14,122
Issue 6: subsequent treatment costs	The company base case applied subsequent treatment costs in line with TA405.	The company base case includes the additional monitoring costs to reflect the SmPC, as requested by the ERG.	Updated ICERs using the additional monitoring costs (full details of model settings are provided in Appendix 4) Trifluridine-tipiracil: £12,744 BSC: £13,607 FOLFOX: £14,187 FOLFIRI: £14,280
Issue 7: ACM adjustments	The company base case did not adjust time on treatment for all-cause mortality	The company base case accepts the changes requested by the ERG and adjusts the time on treatment curve to be consistent with PFS and OS	Updated ICERs using the ACM adjustments (full details of model settings are provided in Appendix 4)

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			Trifluridine-tipiracil: £12,578
			BSC: £13,447
			FOLFOX: £14,015
			FOLFIRI: £14,107

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Clinical expert statement & technical engagement response form

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Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:
- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please return this form by **5pm** on **16 March 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under <u>'commercial in confidence' in turquoise</u>, all information submitted under <u>'academic in confidence' in yellow.</u>If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the <u>Guide to the processes of technology appraisal</u> (sections 3.1.23 to 3.1.29) for more information.

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PART 1 – Treating a patient with previously treated recurrent or metastatic colorectal cancer with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) and current treatment options	
About you	
1. Your name	**John Bridgewater**
2. Name of organisation	**UCL Cancer Institute**
3. Job title or position	**Prof**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with colorectal cancer? ☒ a specialist in the clinical evidence base for colorectal cancer or this technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

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6. If you wrote the organisation submission and/ or do not have anything to add, tick here. <u>(If you tick this box, the rest of this form will be deleted after submission.)</u>	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	-

The aim of treatment for colorectal cancer	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve overall survival (median 20-36 months)
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	We use RECIST criteria, >50% reduction in 1 dimension on imaging

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or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in previously treated recurrent or metastatic colorectal cancer with MSI-H or dMMR?	Yes

What is the expected place of nivolumab plus ipilimumab in current practice?	
11. How is recurrent or metastatic colorectal cancer with MSI-H or dMMR currently treated in the NHS?	COVID NICE recommendations permit the use of nivolumab
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Interim COVID NICE guidance recommend nivolumab or pembrolizumab NCCN guidance https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	No

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	state if your experience is from outside England.)	
•	What impact would nivolumab plus ipilimumab have on the current pathway of care?	Addition of ipilimumab likely to be beneficial and formalise COVID guidance.
12. Will nivolumab plus ipilimumab be used (or is it already used) in the same way as current care in NHS clinical practice?		Combination only used temporarily as part of compassionate use program from BMS.
•	How does healthcare resource use differ between nivolumab plus ipilimumab and current care?	The addition of 4 doses of ipilimumab to 4 weekly nivolumab that is currently being used. The submission is for "3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks." The efficiencies and economies gained through COVID should not be lost.
•	In what clinical setting should nivolumab plus ipilimumab be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
•	What investment is needed to introduce nivolumab plus	None

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ipilimumab? (For example, for facilities, equipment, or training.)	
13. Do you expect nivolumab plus ipilimumab to provide clinically meaningful benefits compared with current care?	Yes, 24 month 79% OS c.f. Venook 2017 60%
• Do you expect nivolumab plus ipilimumab to increase length of life more than current care?	Yes
• Do you expect nivolumab plus ipilimumab to increase health-related quality of life more than current care?	Yes
14. Are there any groups of people for whom nivolumab plus ipilimumab would be more or less effective (or appropriate) than the general population?	MSI patients
The use of nivolumab plus ipilimumab	

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15. Will nivolumab plus ipilimumab be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Toxicity significantly less (as per COVID guidance) 4-weekly schedule established
16. Will any rules (informal or formal) be used to start or stop treatment with nivolumab plus ipilimumab? Do these include any additional testing?	No
17. Do you consider that the use of nivolumab plus ipilimumab will result in any substantial health-related benefits that are unlikely	No

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to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider nivolumab plus ipilimumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
• Is nivolumab plus ipilimumab a 'step-change' in the management of the condition?	Yes
• Does the use of nivolumab plus ipilimumab address any particular unmet need of the patient population?	Yes, 4% of the population will have the opportunity for long term survival.
19. How do any side effects or adverse effects of nivolumab plus ipilimumab affect the	<10% significant toxicities however QoL significantly improved compared to chemotherapy.

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management of the condition and the patient's quality of life?	
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	In COVID guidance
• If not, how could the results be extrapolated to the UK setting?	-
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

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21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Position for POL-E/POL-D patients. BMS do not have a position on this and this should be resolved. These patients are uncommon and should not be neglected because of process.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA405, TA307, TA242, TA105, TA61]?	No
23. How do data on real-world experience compare with the trial data?	Equivalent outcomes (Lam et al ESMO abstract 2020)
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

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24b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions

Current treatment 25. Please complete the following table, informing us of the proportion of patients with previously treated recurrent or metastatic colorectal cancer with MSI-H or dMMR currently receiving each treatment in clinical practice.		

Treatment	Proportion of patients
Single-agent irinotecan	0
FOLFIRI	45%
FOLFOX	45%
Raltitrexed	2%
Trifluridine-tipiracil	2%
Best supportive care	6%

NB N/A because of current NICE COVID guidance

Subsequent treatments

26a. Please complete the first table, informing us about subsequent treatment following second-line treatment for

	Second-line treatment			
	Nivolumab plus ipilimumab	**FOLFOX**	**FOLFIRI**	**Trifluridine-tipiracil**
Proportion having subsequent treatment				
Proportion	0	47%	47%	6%
Distribution of subsequent treatments				
Trifluridine-tipiracil	6%	6%	6%	-
Regorafenib	0	-	-	-
Cetuximab	0	-	-	-
Panitumumab	0	-	-	-

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recurrent or metastatic colorectal cancer with MSI-H or dMMR.	Best supportive care	90%	94%	94%	-
	Other (please specify)	4% trials			

26b. The company used the distribution of subsequent treatments from TA405 (trifluridine–tipiracil for previously treated metastatic colorectal cancer), published in August 2016. Is this distribution likely to reflect current clinical practice?

26c. Please complete the second table, informing us about the approximate duration of subsequent treatment, after second-line treatment.

Subsequent treatment	Approximate treatment duration
Trifluridine-tipiracil	2 months
Regorafenib	-
Cetuximab	-
Panitumumab	-
Best supportive care	N/A
Other (please specify)	

Indirect treatment comparison heterogeneity

27. The ERG identified several differences between the trials in

- 4% advanced disease
- N/A as NICE not approved
- ~50% but N/A
- Prior treatments unlikely to be significant if performance status maintained

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the company's indirect treatment comparison: • Proportion of patients with MSI-H/dMMR CRC • Proportion of patients having prior treatment with bevacizumab or regorafenib • Proportion of patients with KRAS-mutated CRC • Number of prior treatments To what extent are these differences likely to impact the comparability of CheckMate 142 and the comparator studies?	

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PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Indirect treatment comparison Is the partially adjusted matching-adjusted indirect comparison (company preference) or naïve indirect treatment comparison (ERG preference) more relevant for decision making?	Uncertain what these terms refer to
Key issue 2: Stopping rule	No issue

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Does the company preference (2-year stopping rule) or ERG preference (no stopping rule) best reflect how nivolumab plus ipilimumab would be used in clinical practice?	
Key issue 3: Survival extrapolations Which survival extrapolations are most appropriate for decision making? • Company: Semi-parametric model using KM curve to 6.44 months • ERG: Semi-parametric model using KM curve to 2.99 months	-
Key issue 4: Progression-based utility values	-

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Which source of utility values is most appropriate for progression-based utilities? • Company: Taken from TA242. Pre-progression utility of 0.75; Post-progression utility of 0.69 • ERG: Taken from CORRECT publication. Pre-progression utility of 0.74; Post-progression utility of 0.59	
Key issue 5: Utility approach Which utility approach is most appropriate? • Company: Utilities according to treatment status for nivolumab plus ipilimumab, and progression status for the comparators	-

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• ERG: Utilities according to progression status for all treatments, using the values from CORRECT	
Key issue 6: Subsequent treatment Do the subsequent treatment scenarios explored by the company (a one-off cost derived from TA405 for all treatment arms, and a weekly cost calculated from this one-off cost) reflect subsequent treatments in clinical practice?	Yes Uptake of TA405 low
Key issue 7: Adjustment for all-cause mortality Is the way in which the company have adjusted for all-cause mortality appropriate?	-

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Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages	

16. In up to 5 sentences, please summarise the key messages of your statement:

- Transformational therapy with previously unseen long term survival

- Significant minority of patients have serious toxicities but as a whole extremely well tolerated with excellent QoL

- Because of COVID guidelines, experience with nivolumab well established

- "Ipi-light" schedule appears to confer added benefit with minimal added toxicity

- Compassionate use programme has already resulted in a significant number of patients now alive and well who would otherwise have died

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Patient expert statement and technical engagement response form

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

Thank you for agreeing to give us your views on this nivolumab plus ipilimumab and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with colorectal cancer.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Patient expert statement
Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]
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If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **16 March 2021**

Completing this form
Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement
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- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

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Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]
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PART 1 – Living with or caring for a patient with recurrent or metastatic colorectal cancer, and current treatment options	
About you	
1.Your name	**Tom Bartlett**
2. Are you (please tick all that apply):	☒ a patient with this condition? ☒ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Bowel Cancer UK

4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible)
	 ☐ Yes, my nominating organisation has provided a submission
	     ☐ I agree with it and **do not wish to** complete a patient expert statement
	 ☒ Yes, I authored / was a contributor to my nominating organisations submission
	     ☐ I agree with it and **do not wish to** complete this statement
	     ☒ I agree with it and **will be** completing

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5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience.
	☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience:
	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference
	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference
	☐ I have not completed part 2 of the statement

Living with the condition	
6. What is your experience of living with recurrent or metastatic colorectal cancer? If you are a carer (for someone with recurrent or metastatic colorectal cancer) please share your experience of caring for them.	Living with metastatic colorectal cancer is difficult but physically manageable. Life with mCRC has become much better since I began immunotherapy with IPI+NIVO The aspects of this condition that are most challenging to live with are fear of recurrence and the anxiety it causes. As a patient with mCRC you are often worried that the cancer will return and unsure what a different pain or feeling in our body might mean. You become very anxious around scan results and before appointments with the doctor. Side effects are a fact of life as an mCRC patient and you learn to manage them. I have suffered memory loss as a result of Folfiri chemotherapy. While I was on chemotherapy certain activities were difficult, particularly outdoor activities and going to work in the cold while I was on Folfox. Exercise was difficult while I was on Folfiri due to my having a PICC line in my arm. Since I have been on IPI+NIVO there are no limits to what activities I can do and side effects have reduced significantly. The most important aspects of my condition to control include anxiety around recurrence and ensuring that I eat and drink the right things. I don't require any

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Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]
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	support for daily living on IPI+NIVO. While I was on Folfiri chemotherapy I had visits from the district nurse every fortnight to help administer my medication

Current treatment of recurrent or metastatic colorectal cancer in the NHS

7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	There are relatively few current treatment options for MSI-High mCRC patients. Folfox and Folfiri are the only options for KRAS mutant patients besides Lonsurf. Both Folfox and Folfiri have only limited effectiveness, ranging from no effect at all to cancer progressing within a few months of treatment starting. Side effects of chemotherapy can include severe peripheral neuropathy, frequent stomach pains and nausea as well as brain fog, memory loss and severe fatigue. Other MSI high patients I know have reported similar experience with current treatments including shock at the lack of options available, treatments having little or no effect on the progression of the disease and also a number of debilitating side-effects such as chronic fatigue and nausea.
8. If there are disadvantages for patients of **current NHS treatments** for recurrent or metastatic colorectal cancer (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Disadvantages of current treatments include side effects and how treatment is given. Side-effects of current chemotherapy treatment such as peripheral neuropathy, fatigue, brain fog, nausea and stomach pains can make daily living difficult and limit your capacity to work. This can occasionally lead to isolation, anxiety and psychological trauma. For the first six months of my chemotherapy treatment I was unable to go to work due to side effects and became very anxious. Over time however I learned how to manage both the side effects and the anxiety better and was able to return to work on a limited basis within 6 months of starting chemotherapy. Folfiri chemotherapy is given every two weeks and involves wearing a Picc line and carrying around a pump which limits movement and independence. During my chemotherapy treatment I was reliant on my wife's support for basic tasks such as showering and getting items from the fridge

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Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]
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Advantages of nivolumab plus ipilimumab	
9a. If there are advantages of nivolumab plus ipilimumab over current treatments on the NHS please describe these. For example, the impact on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does nivolumab plus ipilimumab help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	Advantages of IPI+NIVO include 1. Remarkable effectiveness - within 3 months all of my tumours had disappeared on my scans 2. Minimal side-effects - IPI+NIVO is much gentler on the body than chemotherapy 3. Within months of starting treatment I was able to lead a normal full life without the worry and effort of frequent hospital visits. This allowed me to return to work full time, to travel freely and visit friends and family. The most important of these advantages was the complete disappearance of all traces of cancer. After 15 months of watching my cancer getting worse and worrying about what might come next, the realisation that I might be able to go back to living a normal life was a truly incredible feeling IPI+NIVO in my experience has proven highly effective in treating widespread metastatic cancer, something which current treatments have failed so far to do. Equally, it has proven to be relatively gentle on the body with a few side-effects. This has allowed me to live a normal independent life free from worry pain and discomfort
Disadvantages of nivolumab plus ipilimumab	
10. If there are disadvantages of nivolumab plus ipilimumab over current treatments on the NHS please describe these? For example, are there any risks with nivolumab plus ipilimumab? If you are	I am aware that there is a risk of auto-immune related side effects with IPI+NIVO, in particular colitis. I have not developed any such side-effects to date in nearly 2 years on the drug. It is right to be concerned about such serious side-effects. However it is also true to say that the dosage improvements which have been made in recent years, in particular the introduction of the low-dose IPI, have had a positive impact here and

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concerned about any potential side affects you have heard about, please describe them and explain why.	will continue to reduce the risk of serious side-effects from IPI+NIVO over the coming months and years.

Patient population

11. Are there any groups of patients who might benefit more from nivolumab plus ipilimumab or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients with MSI high tumours will benefit more from this treatment. MSI stable or MSI low patients tend to benefit very little if at all.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	I am not sure if access to this drug is equal across the country. I was a patient in a major research hub, Oxford University Hospitals and was their first IPI+NIVO mCRC patient. I don't know whether being a patient in a major research hub might make this treatment more accessible compared to other hospitals.

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Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in [the NICE equality scheme](#) More general information about the Equality Act can and equalities issues can be found at [https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real](#) and [https://www.gov.uk/discrimination-your-rights](#).	

Other issues	
13. Are there any other issues that you would like the committee to consider?	Recent developments in genetic profiling have enabled doctors to more accurately identify those patients who should respond well to IPI+NIVO. This will enable it to be used in a more targeted manner towards patients who are more likely to benefit. This contrasts with chemotherapy which is a one size fits all approach.

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PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement

We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

14. What are the main benefits of nivolumab plus ipilimumab for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured?	Advantages of IPI+NIVO include 1. Remarkable effectiveness - within 3 months all of my tumours had disappeared on my scans 2. Minimal side-effects - IPI+NIVO is much gentler on the body than chemotherapy 3. Within months of starting treatment I was able to lead a normal full life without the worry and effort of frequent hospital visits. This allowed me to return to work full time, to travel freely and visit friends and family.

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15. Are there any important issues that have been missed in ERG report?	Many mCRC patients resort to expensive and painful surgeries after chemotherapy stops working in an attempt to slow cancer progression. With this in mind, it is important to also consider the benefits that successful treatment with IPI+NIVO brings in terms of reduced cost of subsequent surgeries and/or radiation treatment, as well as improved quality of life.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- IPI+NIVO is highly effective at treating metastatic colorectal cancer in comparison to current treatments
- IPI+NIVO is gentler on the body than current treatments
- Unlike traditional chemotherapy IPI+NIVO is not debilitating allowing the patient to live a normal independent life
- IPI+NIVO has transformed my life and give me hope of a future free from cancer
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

…………………………………………………………………………………………………….

Your privacy

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……………………………………………………………………………………………………….

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Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]
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Patient expert statement and technical engagement response form

Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]

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- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

-

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Patient expert statement
Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1332]
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Please return this form by **5pm** on **16 March 2021**

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PART 1 – Living with or caring for a patient with recurrent or metastatic colorectal cancer, and current treatment options	
About you	
1.Your name	**Claire Donaghy**
2. Are you (please tick all that apply):	☐ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Bowel Cancer UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

Patient expert statement
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5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience.
	☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience:
	I have been working with Bowel Cancer UK for more than three years and during this time I've been gathering the experiences of bowel cancer patients. The charity does this through case studies (published on our website), through patient days, an online forum, social media groups, engagement with healthcare professionals and from patient surveys.
	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference
	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference
	☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with recurrent or metastatic colorectal cancer? If you are a carer (for someone with recurrent or metastatic colorectal cancer) please share your experience of caring for them.	I do not have personal experience of bowel cancer but people affected by the disease tell us that a diagnosis of bowel cancer is life changing and can affect almost every aspect of daily life, not only for the individual diagnosed but also for their family and loved ones. This is even more acute for those diagnosed at the metastatic stages of the disease, when it is harder to treat and the chance of survival is low (only 1 in 10 people live more than 5 years). It affects them physically, psychologically and socially. It affects their ability to work, to care for family members, to maintain relationships and social activities. If a patient is on chemotherapy, the side effects can be debilitating
	Patients used words like **'devastating', 'tough', 'a battle', 'stressful' and 'difficult'** to describe their overall experience living with advanced bowel cancer

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Current treatment of recurrent or metastatic colorectal cancer in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Current treatment options approved for use on the NHS for metastatic bowel cancer are extremely limited. The impact of this on patients, both on survival and psychologically, is detrimental with many patients unable to access a treatment that could prolong their life. The majority of patients felt that treatment options available on the NHS were 'limited' or 'inadequate' for those with metastatic bowel cancer, especially so for those with high microsatellite instability or mismatch repair deficiency. "*In the context of the latest breakthrough science and research I believe a lot of the treatment options are outdated… these aren't always best options for the patient. The side effects from chemotherapy are devastating.*" "*The bowel cancer with mismatch repair deficiency which I suffered meant only limited drugs were available to actively combat the disease as immunotherapy is not currently approved by NICE. I received chemotherapy treatment (Avastin) which unfortunately didn't work…the cancer increased. I then received Nivolumab (the costs were covered by my medical provider). The improvement following the immunotherapy were apparent within a couple of months.*" "*I feel (NHS) treatment options for those with bowel cancer are limited and the most effective treatments need to be made more widely available.*" "*Poor, colon cancer second biggest killer, … most current treatments are 20 to 30 years old, folfiri, folfox! And existing treatments don't seem to work very well.*"
8. If there are disadvantages for patients of **current NHS treatments** for recurrent or metastatic colorectal cancer (for example how the treatment is given or	Metastatic bowel cancer patients often experience painful side effects while going through current NHS (chemotherapy) treatments including: extreme tiredness; skin toxicities that can cause extremely painful red skin rashes and fissures; dry and peeling skin across hands, feet and face; cystic, painful acne-like spots; severe paronychia; loss of eye lashes and eye soreness; nausea; diarrhoea; reduced appetite.

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taken, side effects of treatment etc) please describe these	Patients have also emphasised the psychological impact continued treatment has had. Many patients have described how their side effects have left them feeling debilitated, isolated and self-conscious. Our community said:
	"In December 2017, treatment was commenced with chemotherapy (FOLFIRI) and a biological targeted therapy - panitumumab. Despite a rocky start with severe side effects of diarrhoea, abdominal pains, fatigue, severe neutropenia and skin rash, 6 cycles were completed with a dose titration. A CT scan concluded a phenomenal response with marked regression of multiple tumours in the liver."
	"I started treatment in October 2019. I had Folfox and Panitumumab….My skin was incredibly dry and despite the constant use of moisturiser, I was like a walking Head and Shoulders advert……I became incredibly sensible to extremes of temperature. I was tired, almost constantly exhausted.
	"I was covered in spots, all over my scalp and face. It spread to my chest and back. I would wake up each morning with blood on my pillows and throughout my treatment it got worse. Some days I was literally peeling my face off my pillow…. As time progressed this got me more and more depressed. I know it is horrible but I had to comb through my beard trying to gently remove the dried blood and puss. It was painful and made me feel embarrassed.
	I also lost a lot of the feeling in my hands and feet, which still has yet to return….My memory has been badly affected. I struggle with names and lose track of what I have been saying, as well as struggle to concentrate."

Advantages of nivolumab plus ipilimumab

9a. If there are advantages of nivolumab plus ipilimumab over current treatments on the NHS please describe these. For example, the impact on your quality of life, your ability to continue work, education, self-care, and care for others?	Patients have told us that this treatment offers them greater hope, additional treatment choice, extended life and less debilitating side effects of medicines that may not work for their genetic profile. The absence of side effects like vomiting, diarrhea and fatigue means patients have a better quality of life. Another benefit is the speed and duration of the treatment.
	Another advantage is that the treatment time is also shorter and less frequent. This means fewer hospital visits, reduction in travel time and cost.
	These advantages allow people to have a better quality of life. For some, this means continuing to (or returning to) work, others can experience seeing their families grow and

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9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?
 	
9c. Does nivolumab plus ipilimumab help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.
	survive to see important life events (such as marriage, birth or graduation).
	
	What a patient considers the most important is very much down to each individual. But the following are all important
	   1. Length of survival
	   2. Quality of life
	   3. Shorter treatment times, less frequent hospital visits
	   4. Absence of debilitating side effects
	
	Some patients will suffer some toxicities from nivolumab plus ipilimumab, however many suffer none of the side effects listed in 8 above. Patients said:
	
	"There will always be potential side-effects/toxicities, but these are less can be more condensed than chemo and much more tolerable in my experience."
	
	"These treatments target the cancer differently, with some incredible results in comparison to the traditional chemotherapy that's routinely offered on the NHS. The side effects are less intrusive, and the treatment is administered in a considerably shorter time period. Chemo can be plugged in for over 48 hours, immunotherapy can be all done within an hour."
	
	"The huge benefit to the patient's quality and extended life. The cost and time saving benefits for the NHS"
	
	*"Advantages: quicker intravenous applications, longer intervals between treatments, next to nothing in terms of side effects. I can work and interact with others as normal (unlike chemotherapy). Most importantly… **I live**, and the disease is currently dormant!"*

Disadvantages of nivolumab plus ipilimumab	
10. If there are disadvantages of nivolumab plus ipilimumab over current treatments on the NHS please describe these? For example, are there any	Patients see the potential disadvantages as follows : *"Some evidence of longer term issues e.g. adrenal gland issues, colitis."* *"The length of time it worked for me"*

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risks with nivolumab plus ipilimumab? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	*"Very expensive. Still unpredictable in terms of the response. A few people have had hyper progression"* *"I have not experienced any disadvantages - the immunotherapy eased my pain, successfully treated the cancer and enabled me to return to full time work."*

Patient population	
11. Are there any groups of patients who might benefit more from nivolumab plus ipilimumab or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Answered in patient organisation submission.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and treatment? Please explain if you think any groups	Answered in patient organisation submission.

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of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.

Other issues

13. Are there any other issues that you would like the committee to consider?

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PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

| 14. What are the main benefits of nivolumab plus ipilimumab for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured? | This treatment option offers hope to patients, who normally survive less than 12 months from diagnosis Life expectancy can be increased by amounts of time that can allow patients to watch family grow, experience important life events and achieve their dreams Quality of life of patients is often much higher than those receiving current NHS treatments, which have high toxicities and debilitating side effects Treatment regimes are often easier than current treatments, with less hospital time. |

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15. Are there any important issues that have been missed in ERG report?	Not that I can think of.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- A diagnosis of bowel cancer can be life changing for those diagnosed, as well as their friends and family, and is even more acute for those at the metastatic stage of the disease when it is harder to treat and there is a low chance of survival.

- Current treatment options approved for use on the NHS for advanced bowel cancer are extremely limited with many patients unable to access a treatment that could prolong their life.

- Patients told us that this treatment offers them greater hope, added months and years of life, additional treatment choice and fewer side effects than chemotherapy, giving them better quality of life.

- Patients felt those who have bowel cancer with mismatch repair deficiency or similar, those newly diagnosed with the disease and younger people would benefit most from this treatment.

All patients should have access to personalised, tailored treatment that is right for them. If outcomes for people with metastatic bowel cancer are to improve, a one-size fits all approach to treating people with the disease will not work.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……………………………………………………………………………………….

Your privacy

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The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

…….

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ERG response to technical engagement

March 2021

1   Introduction

This document provides the Evidence Review Group's (ERG's) critique of the company's response to technical engagement (TE) for the appraisal of nivolumab with ipilimumab (NIVO+IPI) for previously treated metastatic colorectal cancer (mCRC) with high microsatellite instability (MSI-H) or mismatch repair deficiency [ID1332]. The company's updated base case analyses are outlined in Section 2. Each of the issues outlined in the TE report are discussed in detail in Section 3. The ERG's updated base case analyses are given in Section 4.

2   Company's revised cost-effectiveness results

In response to the TE report, the company presented updated base case analyses. The changes that have been made to the company's base case analyses include:

- Utilising the updated database lock (███████████) to update:
  - Comparator outcomes based on the matching adjusted indirect comparison (MAIC) (partially adjusted analysis);
  - NIVO+IPI progression-free survival (PFS) extrapolation (semi-parametric model including 6.44 months of Kaplan Meier [KM] data then a log-logistic distribution);
  - NIVO+IPI overall survival (OS) extrapolation (semi-parametric model including 6.44 months of KM data then a log-normal distribution);
  - NIVO+IPI time-on-treatment (ToT) extrapolation (semi-parametric model including 6.44 months of KM data then a Gompertz distribution);
  - Treatment-specific on-treatment utility for NIVO+IPI (█████);
  - Dose intensity for NIVO+IPI (█████ for NIVO+IPI and █████ for NIVO maintenance);
- Removing the NIVO stopping rule;
- Evaluating the full NIVO+IPI survival model as a relative survival model (PFS, OS and ToT outcomes); and,
- Applying additional monitoring for NIVO+IPI to reflect the Summary of Product Characteristics (SmPC)[1].

The latter three points were suggested by the ERG in the main ERG report. Additionally, the company revised the patient access scheme (PAS) discount on the list price of NIVO from █████ to █████. The PAS discount on the list price of IPI remains at █████. The company's revised base case

results are presented in Table 1 and Table 2. Results including the PAS discount for trifluridine-tipiracil (TRI-TIP) can be found in the confidential appendix.

Table 1. Company's revised base case results, pairwise

Technologies	Total costs	Total LYs*	Total QALYs	Inc. costs	Inc. LYs*	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■	■	■	-	-	-	-
TRI-TIP	£17,020	1.000	0.689	■	■	■	£15,743
Comparison B							
NIVO+IPI	■	■	■	-	-	-	-
BSC	£9,546	0.691	0.477	■	■	■	£16,323
Comparison C							
NIVO+IPI	■	■	■	-	-	-	-
FOLFOX	£12,564	1.546	1.029	■	■	■	£17,220
Comparison D							
NIVO+IPI	■	■	■	-	-	-	-
FOLFIRI	£12,289	1.931	1.287	■	■	■	£17,981

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

*LYs undiscounted

Table 2. Company's revised base case results, fully incremental

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
Step 1					
BSC	£9,546	0.477	▮	▮	-
FOLFIRI	£12,289	1.287	■	■	£3,386
FOLFOX	£12,564	1.029	■	■	Dominated
TRI-TIP	£17,020	0.689	■	■	Dominated

NIVO+IPI	██	██	██	██	£15,743
Step 2					
BSC	£9,546	0.477	█	█	-
FOLFIRI	£12,289	1.287	██	██	£3,386
NIVO+IPI	██	██	██	██	£17,981

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; IPI, ipilimumab; LYs, life years; NIVO: nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

The company also provided revised probabilistic results using 1,000 simulations. These results are given in Table 3. Scatterplots and cost-effectiveness acceptability curves (CEACs) can be found in Figures 1-8 of the company TE response, Appendix 4. Based on these analyses, the probability that NIVO+IPI is cost-effective versus TRI-TIP, best supportive care (BSC), FOLFOX and FOLFOX is ██ at a willingness-to-pay (WTP) threshold of £50,000. As per the original model, the probabilistic results are similar to the deterministic results, and a limitation of the probabilistic analysis is that it takes several hours to run. When the ERG ran the company's probabilistic analysis using 500 simulations it could generate similar results to the company.

Table 3. Company's revised probabilistic base case results (adapted from Table 4 of Appendix 4)

Technologies	Total costs	Total LYs*	Total QALYs	Inc. costs	Inc. LYs*	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	██	██	██	-	-	-	-
TRI-TIP	£17,323	1.029	0.708	██	██	██	£15,934
Comparison B							
NIVO+IPI	██	██	██	-	-	-	-
BSC	£9,537	0.723	0.498	██	██	██	£16,543
Comparison C							
NIVO+IPI	██	██	██	-	-	-	-
FOLFOX	£13,194	1.560	1.039	██	██	██	£17,344
Comparison D							

NIVO+IPI	■■■	■■■	■■■	-	-	-	-
FOLFIRI	£11,487	1.966	1.307	■■■	■■■	■■■	£18,350

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc, incremental; IPI: ipilimumab; LYs, life years; NIVO, nivolumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

*LYs undiscounted

3 Key issues for engagement

3.1 Key issue 1: Indirect treatment comparison

The company has provided updated results for the indirect treatment comparisons (ITC) using data from the CheckMate 142 ■■■■■■■■ database lock. The company presents results of the naïve, partially adjusted and fully adjusted (all reported covariates) comparisons. Of these analyses the company maintains that the partially adjusted MAICs are the most relevant analyses for decision making.

Using the latest data cut for CheckMate 142 the company has been able to adjust for more covariates than was possible in the original submission. That is, the company could use the primary or secondary covariate set rather than the fallback set (adjusting for sex and age only) and still maintain a reasonable effective sample size (ESS > 20). The results of the partially adjusted analyses using the latest data cut for CheckMate 142 could be considered more reliable and less biased than the results of the partially adjusted analysis based on the original data cut for CheckMate 142.

In addition to the choice of covariate set adjusted for, the results of the MAICs also depend on the company's survival extrapolation of NIVO+IPI. For the updated analyses, the company has maintained the base case survival modelling using semi-parametric survival models with KM data up to 6.44 months followed by a standard parametric distribution. Only events after the 6.44-month timepoint inform the survival extrapolation and the company therefore set a minimum threshold of a scaled number of events of 5, below which fitting on the fully adjusted sets would not be attempted. For all the fully adjusted analyses the ESS was less than 20 and the scaled number of events was less than 5 after 6.44 months. Thus, the company did not consider the full adjusted data sets accurate enough to include in the analyses and cost-effectiveness results have therefore not been presented for the fully adjusted analyses.

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Based on the data from the latest data cut for CheckMate 142, the ERG agrees with the company's modelling approach of using KM data to inform the first 6.44 months followed by a standard parametric distribution thereafter (see Key Issue 3). However, the ERG notes that survival extrapolation from an earlier timepoint would have led to more events informing the survival extrapolation, which is likely to have enabled extrapolation of the fully adjusted data. In addition, the ERG does not agree with the parametric distributions chosen by the company for the extrapolation of OS, which is likely to have an impact on the MAIC results (see Key Issue 3).

In the original submission there was little difference between the naïve and partially adjusted comparisons. Primarily because for most comparisons only a very small number of factors had been adjusted for (fallback covariate set: age and sex). With the updated data cut of CheckMate 142 and a larger number of covariates adjusted for, the partial adjustments provided by the company have had a larger impact on both PFS and OS for the comparators (company TE response Appendix 3, Table 1 and 2). Despite this, the cost-effectiveness results based on the naïve comparisons and partially adjusted MAICs are very similar (Table 4).

Table 4. MAIC outcomes vs unadjusted outcomes using the ▮▮▮▮▮▮▮▮ database lock

| Analysis | Outcome | Mean survival (months) or ICER (£/QALY) for NIVO+IPI vs comparator | | | |
		TRI-TIP	BSC	FOLFOX	FOLFIRI
Base case (partially adjusted MAIC)	PFS	5.1	2.5	4.9	10.3
	OS	11.9	8.2	18.4	23.1
	ICER	£15,743	£16,323	£17,220	£17,981
Unadjusted outcomes (naïve comparison)	PFS	3.7	1.8	5.5	6.8
	OS	10.4	7.2	17.3	15.7
	ICER	£15,555	£16,231	£17,127	£17,098

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year

The updated data cut for CheckMate 142 has decreased the uncertainty around the absolute benefits of NIVO+IPI treatment in the MSI-H mCRC population. However, some uncertainty remains around the survival extrapolation of the CheckMate 142 data and the estimated mean survival on

NIVO+IPI, which is discussed in Key Issue 3. In addition, the ERG highlights that irrespective of the analysis used for the ITCs (partially adjusted, fully adjusted or naïve comparisons) there is an unquantifiable but likely very large amount of uncertainty around the size of clinical benefit of NIVO+IPI treatment relative to each comparator due to the observational nature of the comparisons and the resulting residual bias (including differences between the studies that haven't or can't be adjusted for). One important difference, but not the only one, between CheckMate 142 and the comparator studies is the population, with comparator data currently only available for the overall mCRC population rather than for patients with MSI-H as in CheckMate 142. Based on clinical expert opinion, the direction of bias due to this difference is expected to favour the comparators. However, the ERG notes that the evidence of the prognostic difference between the MSI-H and overall mCRC populations is mixed. For other factors it is more difficult to predict the direction of the possible bias in the analyses.

The ERG maintains that due to the unanchored nature of the MAICs, the analysis adjusting for all reported covariates provides the most accurate results, although the ERG acknowledges that the imprecision is very large as the results are based on a small ESS. The ERG also acknowledges that the updated partially adjusted MAICs may provide less biased estimates than the naïve comparisons. However, as there is no way of assessing the residual bias or if any of the adjustments have led to a bias reduction, the ERG's preferred approach remains the use of a naïve comparison as it is transparent in terms of the likely biases that exist within the comparison and the analysis itself has not introduced additional bias into the comparison.

In addition, the ERG prefers a different parametric curve to the company for the OS extrapolation of NIVO+IPI (see response to Key Issue 3). In order to avoid the inconsistency of using different extrapolations of NIVO+IPI informing the model and informing the MAICs (and thereby the comparator data informing the model), the ERG prefers the naïve comparison for its base case.

3.2   Key issue 2: Stopping rule

As discussed in the main ERG report, the ERG is of the opinion that the 2-year stopping rule should be removed from the economic analysis as no formal stopping rule was applied during CheckMate 142 or is expected to be in the marketing authorisation. The ERG's clinical experts also fed back that their preference would be to continue NIVO treatment until disease progression and not to take patients off NIVO treatment if they are still deriving a benefit and remain progression-free at 2 years.

In the company's response to TE, the company removed the 2-year stopping rule from its base case analysis. The company also updated the ToT data for NIVO+IPI to reflect the latest database lock of CheckMate 142 (██████████). Figure 1 and Figure 2 present the ToT curves for the February 2019 and the ██████████ database lock, respectively. The company's extrapolation of ToT is discussed under Key Issue 3.

The ERG also considers it important to reiterate that a protocol amendment was implemented in CheckMate 142. This amendment enabled clinicians to stop nivolumab treatment after achievement of maximum clinical benefit. This protocol amendment was implemented in February 2019 and so is not captured at the February 2019 database lock. However, at the ██████████ database lock, the impact of this protocol amendment is better captured.

Overall, the ERG is satisfied that the company's revised approach reflects how NIVO+IPI will be used in clinical practice and better reflects the clinical benefits observed in CheckMate 142.

Figure 1. CheckMate 142: Time on treatment; February 2019 database lock (reproduced from Figure 1 of the company's TE response)
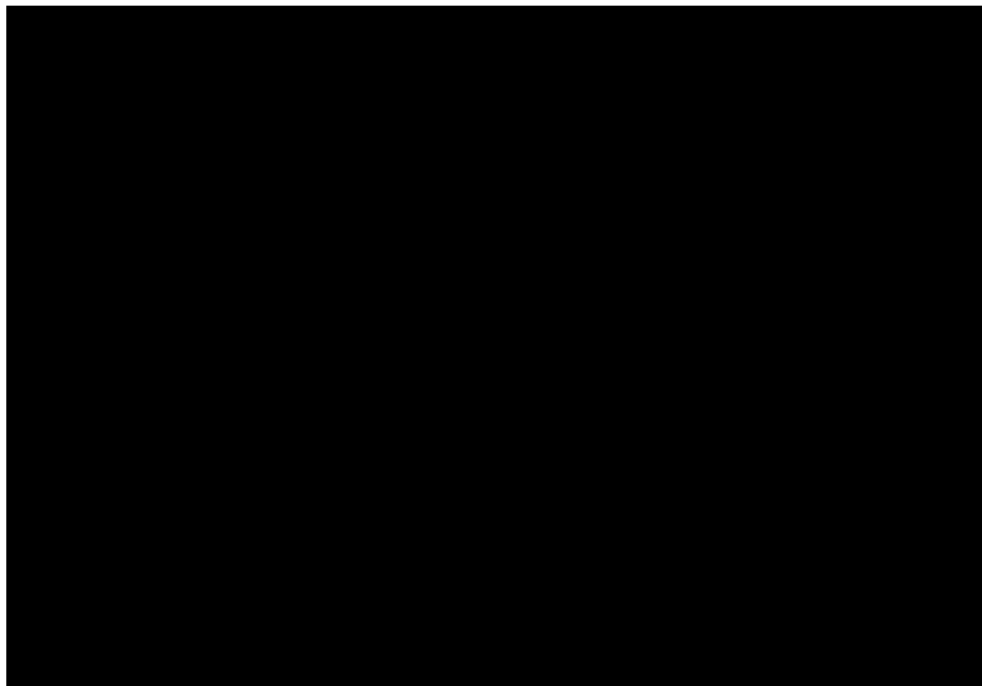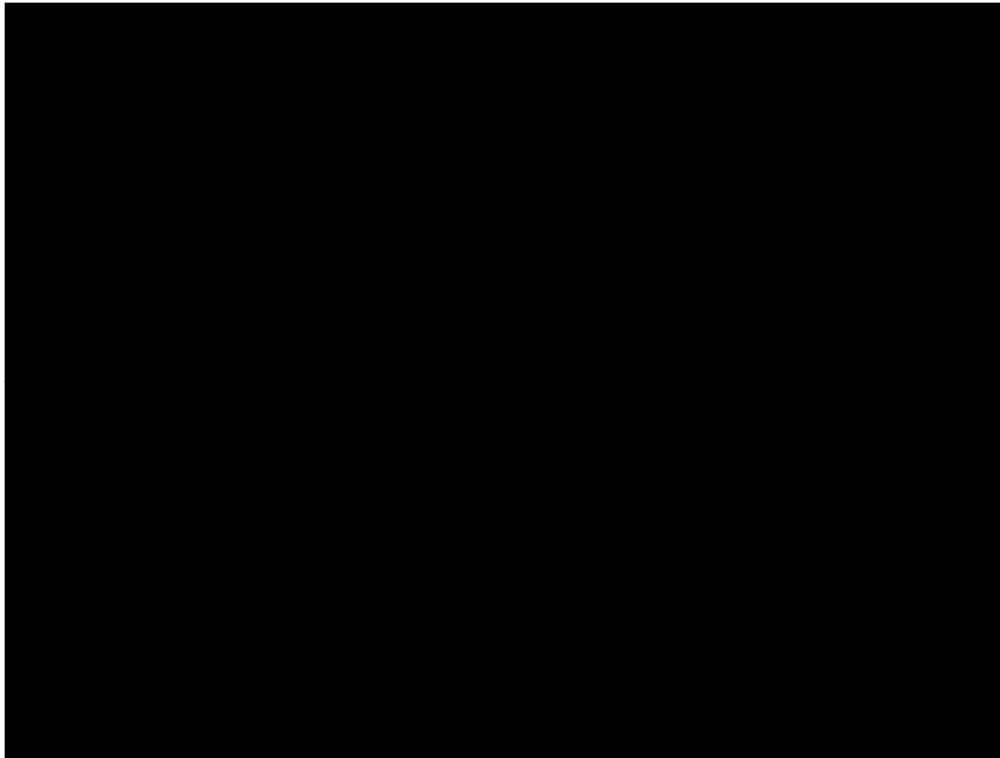
Figure 2. CheckMate 142: Time on treatment; ████████ database lock (reproduced from Figure 2 of the company's TE response)

3.3 Key issue 3: Survival extrapolations

The company has provided updated survival extrapolations using data from the CheckMate 142 *********** database lock. This was done for PFS, OS and ToT outcomes. Table 5 summarises these changes. Figure 3 shows the evolution of the model of PFS by investigator assessment between the February 2019 and *********** database lock.

Figure 4 shows the evolution of the model of OS. Figure 5 shows the dramatic change in the ToT curve resulting from the implementation of treatment stopping protocol after achievement of maximum clinical benefit in CheckMate 142.

Table 5. Summary of changes to survival extrapolations

Survival outcome	Distribution		Mean survival	
	CS (February 2019 DBL)	TE (██████ DBL)	CS (February 2019 DBL)	TE (██████ DBL)
PFS	SP model: 6.44 months of KM data followed by an exponential distribution	SP model: 6.44 months of KM data followed by a log-logistic distribution	6.1 years	9.6 years
OS	SP model: 6.44 months of KM data followed by a log-logistic distribution	SP model: 6.44 months of KM data followed by a lognormal distribution	14.3 years	17.5 years
ToT	SP model: 6.44 months of KM data followed by a log-logistic distribution	SP model: 6.44 months of KM data followed by a gompertz distribution	1.3 years*	2.2 years

Abbreviations: CS, company submission; DBL, database lock; OS, overall survival, PFS, progression-free survival; SP, semi-parametric; TE, technical engagement; ToT, time on treatment

*Including 2-year stopping rule

Figure 3. Progression-free survival by investigator assessment - previous and new base case models applied to CheckMate 142 population (reproduced from Figure 1 of Appendix 1)
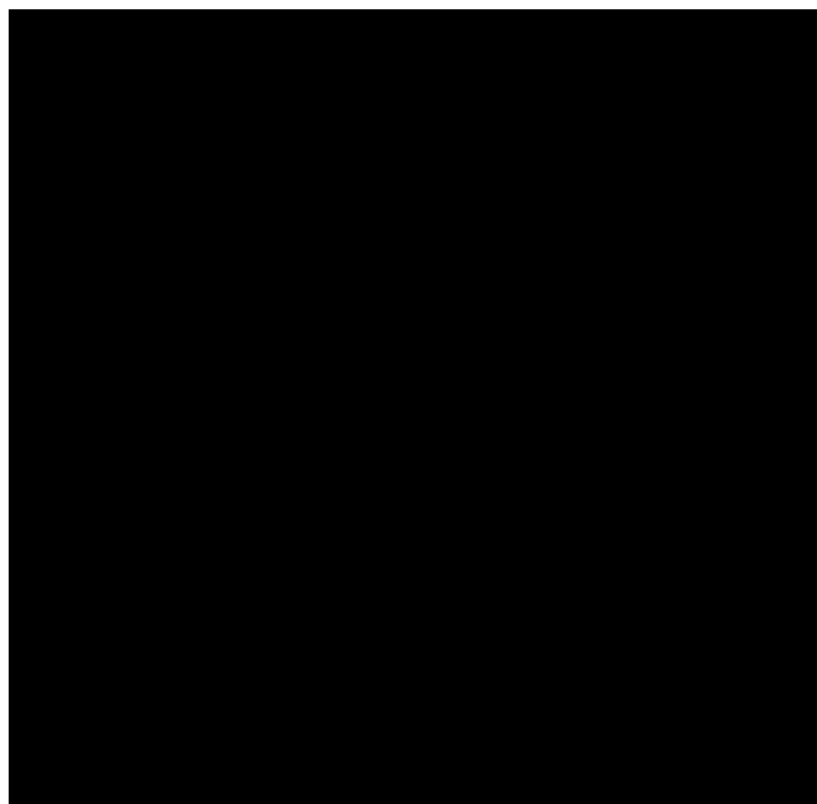
Figure 4. Overall Survival - previous and new base case models applied to CheckMate 142 population (reproduced from Figure 2 of Appendix 1)
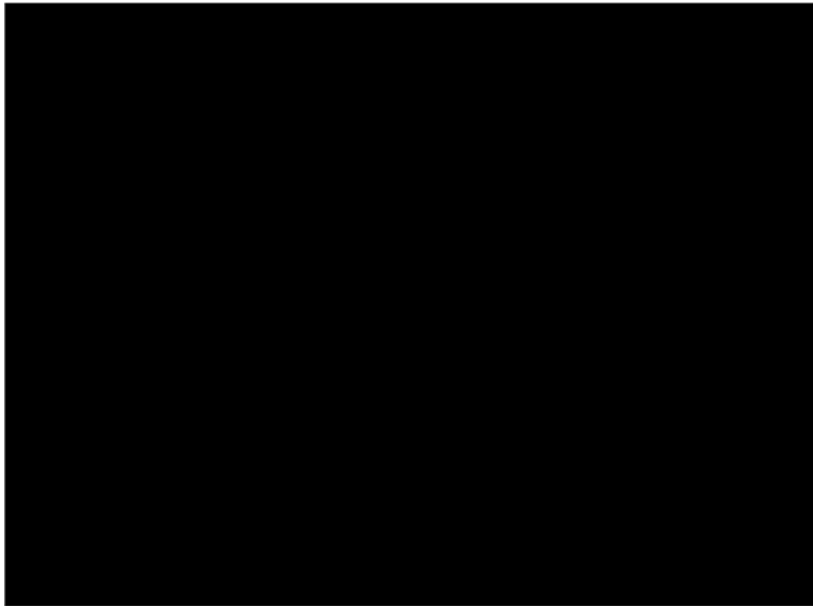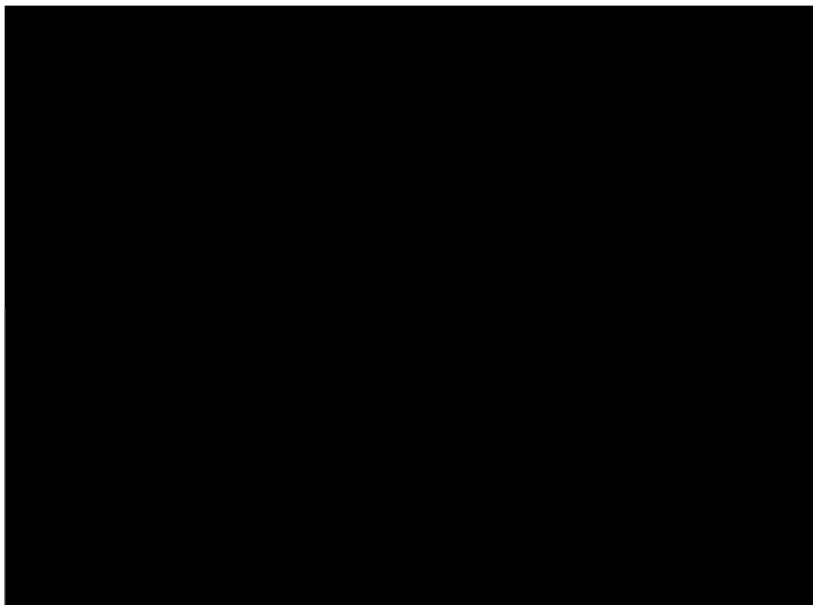

 Figure 5. Time on Treatment - previous and new base case models applied to CheckMate 142 population (reproduced from Figure 3 of Appendix 1)

Using the updated database lock, the company still considered the semi-parametric models using 6.44 months of KM data to be the best fit. As explained in the main ERG report, the ERG was concerned that using 6.44 months of KM data to inform the semi-parametric extrapolation unnecessarily cut the amount of data that can be used to inform the long-term extrapolation.

However, with longer-term data available, the company argues that there is limited rationale to using an earlier cut point to conserve data when the hazard profile continues to evolve.

The company also reiterated that, for PFS, the point at which the hazard profile approached a constant excess was 6.44 months at the earliest. Additionally, the cumulative hazard gradient revealed that the period between 2.99 months and 6.44 months experienced a higher gradient than the average for the remainder of the profile, indicating that the longer-term hazard profile was still developing and its inclusion in a constant excess hazard would be inappropriate (see Figures 3 and 4 in the company's TE response). The ERG accepts the company's rationale for PFS. However, the ERG still considers that the company is using the PFS hazard profile to justify the KM cut-off point for ToT and OS. The ERG maintains that the initial high hazard for ToT and OS approaches a lower, nearly constant value after 3 months.

To address the ERG's concerns the company also provided a sensitivity analysis which evaluated survival curves using 2.99 months of KM data (the ERG's preferred KM cut-off point in the main ERG report). The ERG agrees with the company that the statistical and visual fits are generally worse from this point, and that both time points (2.99 and 6.44 months) produce similar clinical effectiveness outcomes and cost-effectiveness results. These curves and the associated cost-effectiveness results are given in Appendix 4 of the company's TE response. As such, the ERG accepts the 6.44-month KM cut-off point chosen by the company for PFS, ToT and OS.

One issue the ERG would like to raise is the company's revised parametric distribution for OS. Given that the company used the PFS hazard profile to inform the KM cut-off point for OS, the ERG considers that it would be more appropriate to use the same parametric distribution for PFS and OS – the log-logistic. As shown in

Figure 6, the log-logistic and log-normal distributions both have excellent visual and statistical fits (AIC: 277.62 vs 277.22 and BIC: 282.96 vs 282.57 for the log-logistic and log-normal, respectively). The log-logistic distribution was also chosen by the company in their original submission. As shown in the company's scenario analyses (Table 6), applying a log-logistic distribution increases the incremental cost-effectiveness ratio (ICER) for NIVO+IPI by around £400 per quality-adjusted life year (QALY) in each comparison. However, in these scenarios, the link between the NIVO+IPI extrapolations in the economic analysis with the MAIC survival inputs is missing which limits their credibility. This link was discussed in detail in the main ERG report.

Figure 6. OS: semi-parametric (piecewise) relative survival models overlaid upon Kaplan-Meier - 6.44 month cut point (reproduced from Figure 25 of Appendix 1)
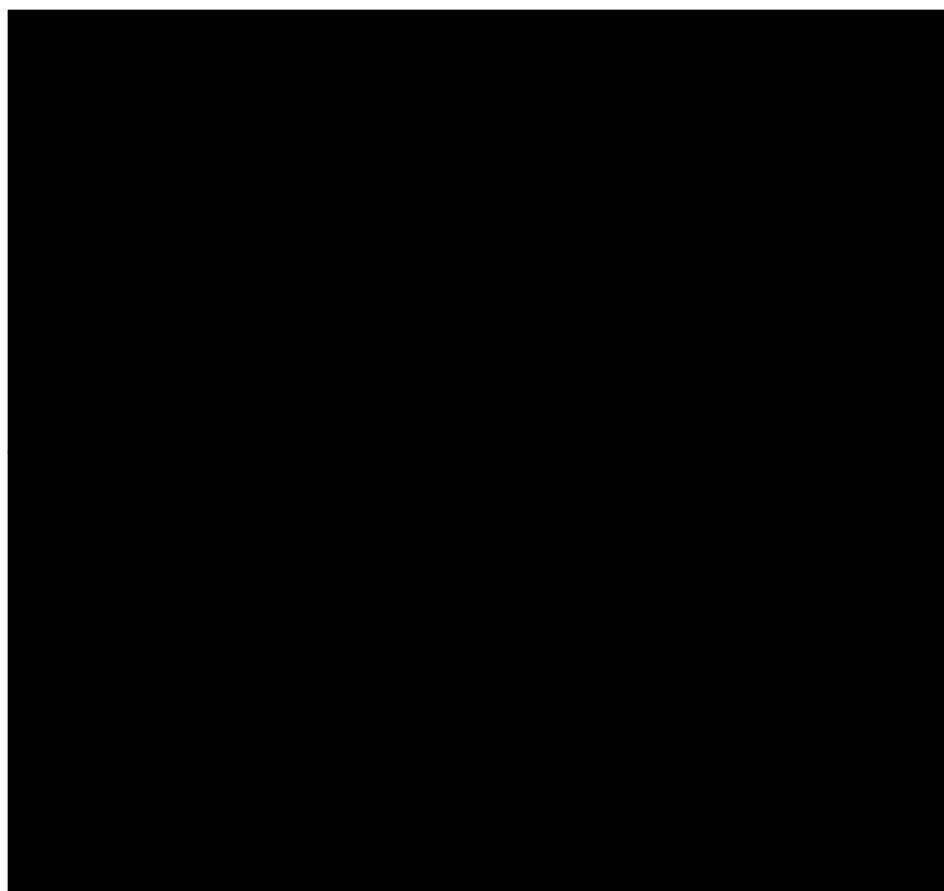

Table 6. Results of the company's scenario analyses, OS distribution

| Technology | NIVO+IPI vs technology ICER (£/QALY) | |
	Base case (log-normal)	Scenario (log-logistic)*
TRI-TIP	£15,743	£16,096
BSC	£16,323	£16,681
FOLFOX	£17,220	£17,637
FOLFIRI	£17,981	£18,440

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; NIVO+IPI, nivolumab with ipilimumab; OS, overall survival; QALY, quality adjusted life year; TRI-TIP, trifluridine-tipiracil

*Scenario impacts the survival of NIVO+IPI in the economic analysis, but this does not cascade down to the MAIC survival inputs

3.4 Key issue 4: Progression-based utility values

During the factually accuracy check, the company explained that the progression-based health state utility values (HSUVs) applied in the economic analysis were taken from TA242 - an appraisal of cetuximab, bevacizumab and panitumumab for the treatment of mCRC after first-line chemotherapy, and not the CORRECT study.[2, 3]

The pre-progression HSUV between the two sources is similar (0.74 vs 0.75, CORRECT and TA242, respectively), but there is a large difference in the post-progression HSUV (0.59 vs 0.69, CORRECT and TA242, respectively). The values identified by the ERG in the CORRECT study were used and accepted in TA405 - an appraisal of TRI-TIP for previously treated mCRC.[4] In the CS, the company provided no rationale for why the values accepted in TA242 were preferred to those in CORRECT.

In the company's response to TE, the company explained that TA242 reflects patients who have previously received first-line treatment. This differs from the CORRECT study where 49% of patients in the regorafenib arm and 47% of patients in the BSC arm had received at least four systemic anticancer treatments for metastatic disease. The company then concluded that the NIVO+IPI arm of CheckMate 142 is more representative of the TA242 population than CORRECT, as 23% of patients had received only one prior treatment and 36% had received only two prior treatments.

The ERG has several issues with the company's rationale. Firstly, the company failed to mention that 40% of patients had received at least three prior treatments in CheckMate 142 (see Table 9 in Document B of the CS). This increases the similarity between patients in CheckMate 142 and CORRECT (according to the number of prior treatment lines). Secondly, the company could not provide the primary source used to inform the utility values in TA242. As such, the ERG has no way of validating the company's assertion that the utility values in TA242 are representative of patient who received one prior line of treatment (or make any comparisons between the study populations). Thirdly, the utility sources preferred by the ERG for TA242 (Mittmann *et al.* 2018[5], a cost-utility study of the CO.17 trial) and company for TA242 (reanalysed estimates of the CO.17 trial) used the Health Utility Index (HUI) to obtain estimates of utility. The HUI deviates from the NICE reference case, which encourages the use of EQ-5D.[6] Finally, as mentioned in the main ERG report, the ERG for TA242 was concerned that the post-progression HSUV (0.69) was too high.

For these reasons, the ERG maintains that utility values by progression status should be taken from the CORRECT study. The ERG's results including these values can be found in Section 4.

3.5   Key issue 5: Utility approach

The company maintains that treatment-specific utilities for NIVO+IPI are appropriate given that the novel mechanism of action of NIVO+IPI drives several key benefits, including improved toxicity and survival, that cause improved quality of life.

The company provided an updated utility value for patients receiving NIVO+IPI using data from the CheckMate 142 ███████████ database lock. As per the original submission, this utility value includes patients receiving NIVO+IPI pre- and post- progression. Table 2 in Appendix 2 shows the number of patients and number of observations included in the derivation of this utility value at each database lock. Figure 7 in Section 6 shows the number of patients on-treatment over time in the company's revised model, according to progression status.

Using the latest data cut for CheckMate 142, the company found that the on-treatment utility value for NIVO+IPI was ██████████████ than in the original submission, which used the February 2019 database lock (██████████████). The company also acknowledged that this was ██████ than the age and sex matched general population matched utility value (Ara and Brazier 2010).[7] For face validity, the company ██████ utility values to that of the general population and considered that a utility similar to the general population is not implausible because a proportion of patients are expected to enter a state of long-term remission. The utility values applied in the company's revised analysis are given in Table 7 (only the on-treatment utility value has been updated).

Table 7. Utility values applied in the company's revised base case analysis

Technology	State	Mean utility
NIVO+IPI	On-treatment	████
	Off-treatment	0.69
Comparators	Pre-progression	0.75
	Post-progression	0.69
*████████ to the utility of the general population		

In the company's TE response, the company also responded to the ERG's clinical expert concerns that the toxicities associated with IPI would have a large negative impact on patients' quality of life. The company explained that there is no evidence to indicate that IPI would be more toxic than

FOLFOX and FOLFIRI and that IPI is given at a lower, more tolerable dose in this combination than in other indications.

Given the uncertainty in application of treatment-specific utilities, the company assessed values from TA242 and the CORRECT study in scenario analysis, where NIVO+IPI utility values were applied by progression status, as opposed to treatment status. Results of the company's scenario analysis are provided in Table 8. ICERs were slightly reduced in comparison to the base case when exploring progression-based utilities from TA242; conversely, ICERs were slightly increased in comparison to the base case when using progression-based utilities from the CORRECT study.

The ERG also adds that these scenarios have a relatively small impact on the ICER because patients spend a shorter amount of time on the high on-treatment utility value (▮▮▮▮) and a longer amount of time on the lower pre-progression utility value (0.75 using TA242 and 0.74 using CORRECT). As such, the QALY is similar. Figure 7 and Figure 8 in Section 6 may aid this interpretation.

Table 8. Results of the company's scenario analyses, utility values by progression status, as opposed to treatment status

Technology	NIVO+IPI vs technology ICER (£/QALY)		
	Base case	Scenario TA242	Scenario CORRECT
TRI-TIP	£15,743	£15,548	£16,639
BSC	£16,323	£16,127	£17,248
FOLFOX	£17,220	£16,996	£18,104
FOLFIRI	£17,981	£17,738	£18,957

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; NIVO+IPI, nivolumab with ipilimumab; QALY, quality adjusted life year; TRI-TIP, trifluridine-tipiracil

Overall, the ERG maintains that, in the absence of a randomised controlled trial with an appropriate comparator arm there is not enough evidence to justify treatment-specific utilities. As such, the ERG considers using utility values according to progression status, from one source (the CORRECT study), to be more appropriate.

3.6 Key issue 6: Subsequent treatment

In the company's response to TE, the company accounted for the additional monitoring associated with NIVO+IPI reported in the SmPC.[1] To do this, the company updated the subsequent treatment cost from £1,621 to £3,752 in the NIVO+IPI arm. This is in line with the company's clarification response and the ERG's preferred assumption in the main ERG report. However, the ERG would like to clarify that treatment-specific monitoring costs and subsequent treatments costs are separate issues (only how they are applied in the model is common to them).

As for subsequent treatment costs in the comparator arm, the company maintained their base case assumption and applied the same one-off subsequent treatment cost upon discontinuation. This cost, £1,621, was taken from TA405.[4] The ERG disagreed with this simplification as the composition and duration of subsequent treatments is likely to differ in each treatment arm. In order to address the ERG's concerns, the company provided three scenarios in their response to TE. Two of these were based on clinical expert opinion and one was based on the subsequent treatment data collected in CheckMate 142. A detailed report of the clinical expert responses is given in Appendix 5 of the company's TE response and a full derivation of the costs in each scenario is given in Appendix 4 of the company's TE response.

In brief, the company made the following assumptions based on clinical expert opinion in their first scenario:

- Patients receiving NIVO+IPI would receive a chemotherapy not previously given (FOLFOX conservatively assumed as it is the most expensive option) for 3.5 cycles;
- Patients receiving FOLFOX or FOLFIRI would go on to receive TRI-TIP for 3 cycles;
- Patients receiving NIVO+IPI who discontinue chemotherapy (FOLFOX) also subsequently receive TRI-TIP for 3 cycles;
- Patients receiving TRI-TIP are assumed to receive BSC for the remainder of their treatment; and,
- All patients end their treatment cycle on BSC.

The company's second scenario explored the impact of subsequent treatments for patients who will have the BRAF mutation. Based on clinical expert opinion, it is assumed that the subsequent treatment pathway is in line with the previous scenario, with the inclusion that one third of patients receiving either NIVO+IPI, FOLFOX or FOLFIRI will go on to receive subsequent encorafenib plus

cetuximab for 18 cycles. In CheckMate 142, 25% of patients had a BRAF mutation. The company also highlighted that encorafenib plus cetuximab has recently been approved by NICE for patients with a BRAF mutation (TA668).[8]

Table 9 summarises the derivation of the weighted cost for subsequent treatments derived from CheckMate 142. Treatment regimens received by more than one patient were included and time on treatment was identified from clinical trials. A weighted average cost of £16,120 was derived. In addition to this, the subsequent cost of BSC from the base case analysis (£3,752 for NIVO+IPI and £1,621 for comparators) was added to generate a subsequent treatment cost of £19,872 for patients receiving NIVO+IPI and £17,741 for patients receiving comparator treatments (with the exception of BSC).

Table 9. Derivation of weighted subsequent treatment cost from CheckMate 142 (adapted from Table 22 of Appendix 4)

Subsequent treatment	Cycle	Cycle length (weeks)	Number of cycles	Total regimen cost	Number of patients receiving subsequent treatment	Weight	Weighted cost
Cetuximab + irinotecan	Cycle 1	1	1.00	£12,548	▮	▬	£16,120
	Cycle 2+	2	8.41				
FOLFIRI	Cycle 1	1	1.00	£3,773	▮	▬	
	Cycle 2+	2	8.55				
FOLFOX	Cycle 1	1	1.00	£3,915	▮	▬	
	Cycle 2+	2	8.85				
Nivolumab	All cycles	2	33.00	£64,439	▮	▬	
Regorafenib	All cycles	4	1.90	£7,485	▮	▬	

Abbreviations: FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin

In all scenarios, drug acquisition costs were taken from the Drugs and pharmaceutical electronic market information tool (eMIT)[9], the Monthly Index of Medical Specialities (MIMS)[10] or the British National Formulary (BNF)[11], administration costs were taken from the NHS National Cost Collection Data[12], and dosing schedules were sourced from the literature using the most relevant sources.

Table 10 summaries the one-off subsequent treatment costs applied in each scenario, while Table 11 provides the resulting ICERs. Although the incremental cost associated with NIVO+IPI increased in each scenario, all ICERs remained below £20,000 per QALY. The comparison with BSC had the largest impact on the ICER given that BSC has no subsequent treatment cost. The ERG also considers it important to highlight that regorafenib, encorafenib plus cetuximab, cetuximab plus irinotecan have commercial arrangements with NICE. Results including these arrangements can be found in the confidential appendix.

Table 10. One-off subsequent treatment costs applied in the company's scenario analyses

Technology	Base case	Clinical expert opinion	Clinical expert opinion including encorafenib + cetuximab for BRAF mutated patients	CheckMate 142
NIVO+IPI	£3,752	£11,728	£24,013	£19,872
TRI-TIP	£1,621	£1,621	£1,621	£17,741
BSC	NA	NA	NA	NA
FOLFOX	£1,621	£8,208	£20,956	£17,741
FOLFIRI	£1,621	£8,208	£20,956	£17,741

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; NA, not applicable; NIVO+IPI, nivolumab with ipilimumab; TRI-TIP, trifluridine-tipiracil

Table 11. Results of the company's scenario analyses, subsequent treatments

| Technology | NIVO+IPI vs technology ICER (£/QALY) | | | |
	Base case	Clinical expert opinion	Clinical expert opinion including encorafenib + cetuximab for BRAF mutated patients*	CheckMate 142
TRI-TIP	£15,743	£16,644	£18,033	£15,837
BSC	£16,323	£17,198	£18,545	£19,088
FOLFOX	£17,220	£17,520	£17,725	£17,549
FOLFIRI	£17,981	£18,214	£18,275	£18,131

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; NIVO+IPI, nivolumab with ipilimumab; QALY, quality adjusted life year; TRI-TIP, trifluridine-tipiracil

*Values in the model differ to those in the company's response documents (Table 7 of the company's main document and Table 2 of Appendix 4), values in the model reported here

The ERG has three key issues with the company's scenarios. One on the duration of FOLFOX when patients discontinue NIVO+IPI and two on the derivation of the cost using data collected in CheckMate 142. Each of these is described in turn below.

Firstly, in the scenarios based on clinical expert opinion, the company assumed a median of 3-4 cycles of FOLFOX when patients discontinue NIVO+IPI. This ignores clinical expert opinion to the company that up to 12 cycles could be given if patients are very fit. Clinical experts also advised the company that patients that progress on chemotherapy are generally less fit than those that progress on an immunotherapy. The ERG also sought clinical expert advice on this issue from its own experts. The ERG was advised that there is no standard duration of treatment as the duration is largely dependent on a patient's progression status. It would be unusual to give a patient more than 12 cycles of a chemotherapy, but it is also unusual to limit a patient to only 3-4 cycles if they remain progression free. Thus, it would not be unreasonable to assume the duration is somewhere in the middle of these estimates if we are considering relatively fit patients progressing after treatment with an immunotherapy.

Similarly, the ERG also notes that, in the company's base case analysis, FOLFOX is given for a median of 4.3 months (equal to 18.7 weeks and around 9 treatment cycles).[13] Given that there is no evidence on using FOLFOX after an immunotherapy and that the company makes the assertion that a proportion of patients can enter long-term remission when they discontinue NIVO+IPI, the ERG considers that it would not be unreasonable to assume FOLFOX is given for the same amount of time when patients discontinue NIVO+IPI. Assuming 9 treatment cycles is also more closely aligned to the ERG's clinical expert opinion.

For these reasons, the ERG considers a median of 3.5 cycles to be too low and explores a scenario using 9 cycles. Results of the ERG's scenario analyses can be found in Section 4.

Secondly, in the scenario based on subsequent treatment data collected in CheckMate 142, the company applied the same one-off cost (£16,120, excluding the addition of BSC) in the NIVO+IPI arm and comparator arms. The ERG considers this to be an unreasonable assumption given that clinical experts to the company and ERG advised that the subsequent treatment regimens depend on the prior line of treatment. An additional area of concern is that the subsequent treatment data collected in CheckMate 142 at the latest database lock is still limited for patients who had discontinued treatment or experienced a progression event. Using the MSI-H cohort assigned to

NIVO+IPI (N=119), ▮ were assessed per investigator to have progressed and only ▮ of those commenced a subsequent treatment. As such, the extrapolations are likely to be extremely unreliable. However, the ERG appreciates the company's attempt to extrapolate the data.

Overall, the ERG considers the company's scenario analysis based on clinical expert opinion, including encorafenib + cetuximab for BRAF mutated patients, to be one step closer to reflecting the subsequent treatments that will be used in clinical practice. Further details on the ERG's preferred assumptions can be found in Section 4.

3.7   Key issue 7: Adjustment for all-cause mortality

In the company's original model, the company applied general population mortality to NIVO+IPI from week 29 (the point of the KM cut-off). This suggests there were deaths from other causes during the CheckMate 142 trial. According to the Decision Support Unit (DSU) Technical Support Document (TSD) 21[14], the company should've separated mortality from CheckMate 142 into that caused by the disease of interest and that due to other causes and then extrapolated both, rather than applying general population mortality to the CheckMate 142 survival curves from week 29.

To address this issue, the company updated their base case analysis at TE so that the full survival model is evaluated as a relative survival model, inclusive of the initial, KM section. The company also noted that, "By removing the trial matched lifetable hazard from these sections, both pieces of the piecewise models of PFS, OS and TOT for NIVO-IPI were made relative survival, and the matched scenario baseline hazard profile was then applied in the economic model over the full time horizon." The ERG is unclear if and how trial matched lifetable hazard from these sections were removed. When the ERG compared the KM data in the original model with revised model for TE, the ERG found that some adjustments had been made to PFS (Table 12). However, these were positive and negative, and no adjustments were made to OS. The ERG expected the probability of survival to be higher for PFS and OS at TE if mortality from other causes was removed from the data.

To explore the impact of this uncertainty, the ERG explored a scenario where general population mortality is applied to the original KM data, from week 0. This is a pragmatic solution and assumes all deaths in the trial were caused by the disease of interest. However, as shown in Section 4, this had a minimal impact on the results.

Table 12. KM data (probability of survival) applied in the company's models

Time (months)	CS PFS	TE PFS	CS +TE OS	CS +TE ToT	Difference in PFS (CS-TE)
0.00	███	███	███	███	0.0000
0.23	███	███	███	███	0.0000
0.46	███	███	███	███	0.0000
0.69	███	███	███	███	0.0000
0.92	███	███	███	███	0.0000
1.15	███	███	███	███	0.0084
1.38	███	███	███	███	0.0084
1.61	███	███	███	███	0.0084
1.84	███	███	███	███	0.0084
2.07	███	███	███	███	0.0084
2.30	███	███	███	███	0.0084
2.53	███	███	███	███	0.0084
2.76	███	███	███	███	0.0084
2.99	███	███	███	███	0.0084
3.22	███	███	███	███	-0.0002
3.45	███	███	███	███	-0.0002
3.68	███	███	███	███	-0.0002
3.91	███	███	███	███	-0.0002
4.14	███	███	███	███	-0.0002
4.37	███	███	███	███	-0.0002
4.60	███	███	███	███	-0.0002
4.83	███	███	███	███	-0.0002
5.06	███	███	███	███	-0.0002
5.29	███	███	███	███	-0.0002

5.52	■■	■■	■■	■■	-0.0002
5.75	■■	■■	■■	■■	-0.0002
5.98	■■	■■	■■	■■	-0.0002
6.21	■■	■■	■■	■■	-0.0002
6.44	■■	■■	■■	■■	-0.0002

Abbreviations: CS, company submission; OS, overall survival, PFS, progression-free survival; SP, semi-parametric; TE, technical engagement; ToT, time on treatment

4   ERG's cost-effectiveness results

In Section 3, the ERG has described several scenarios that warrant further exploration. The scenarios that the ERG has produced are applied to the company's revised base case and include:

- Progression based utility values from CORRECT, maintaining the on-treatment utility value for NIVO+IPI (see Key Issue 4);
- Amending the subsequent treatment cost scenarios based on clinical expert opinion so that patients receive 9 cycles of FOLFOX when they discontinue NIVO+IPI (see Key Issue 6);
    - This increases the on-off cost from £11,728.20 to £13,915.82 when BRAF patients are excluded and from £24,013.17 to £25,471.58 when BRAF patients are included;
- Applying general population mortality to the original KM data on PFS from week 0 (see Key Issue 7).

Results of these scenario analyses are provided in Table 13.

Table 13. Results of the ERG's scenario analyses

Results per patient	NIVO+IPI (1)	TRI-TIP (2)	BSC (3)	FOLFOX (4)	FOLFIRI (5)	Incremental value			
						(1-2)	(1-3)	(1-4)	(1-5)
Company base case									
Total costs (£)	■■	17,020	9,546	12,654	12,289	■■	■■	■■	■■
QALYs	■■	0.689	0.477	1.029	1.287	■■	■■	■■	■■

ICER (£/QALY)						15,743	16,323	17,220	17,981
Progression based utility values from CORRECT, maintaining the on-treatment utility value for NIVO+IPI (see Key Issue 4)									
Total costs (£)	▮	17,020	9,546	12,654	12,289	▮	▮	▮	▮
QALYs	▮	0.631	0.429	0.920	1.182	▮	▮	▮	▮
ICER (£/QALY)						18,018	18,632	19,680	20,687
9 cycles of FOLFOX when patients discontinue NIVO+IPI, excluding BRAF mutations (see Key Issue 6)									
Total costs (£)	▮	17,020	9,546	16,919	17,052	▮	▮	▮	▮
QALYs	▮	0.689	0.477	1.029	1.287	▮	▮	▮	▮
ICER (£/QALY)						16,891	17,437	17,780	18,485
9 cycles of FOLFOX when patients discontinue NIVO+IPI, including BRAF mutations (see Key Issue 6)									
Total costs (£)	▮	17,020	9,546	25,174	26,271	▮	▮	▮	▮
QALYs	▮	0.689	0.477	1.029	1.287	▮	▮	▮	▮
ICER (£/QALY)						18,197	18,704	17,898	18,455
Applying general population mortality to the original KM data on PFS from week 0 (see Key Issue 7)									
Total costs (£)	125,929	17,020	9,546	12,654	12,289	▮	▮	▮	▮
QALYs	▮	0.689	0.477	1.029	1.287	▮	▮	▮	▮
ICER (£/QALY)						15,742	16,323	17,220	17,981

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc., incremental; KM, Kaplan Meier; LYs, life years; NIVO+IPI, nivolumab with ipilimumab; PFS, progression-free survival; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

In this section of the report, the ERG also presents its preferred base case ICER. The key differences between the company's base case ICER and ERG's preferred base case ICER are given in Table 14. The ERG has decided to maintain the company's revised adjustment for all-cause mortality in its

base case analyses (see Key Issue 7). Even though it is unclear to the ERG if the company has made the appropriate adjustment, the ERG's alternative approach had a minimal impact on the results (see Table 13). Thus, if the company made the appropriate adjustment or not, the ERG does not consider it to impact decision making. The ERG also accepts removal of the NIVO stopping rule (see Key Issue 2). Table 15 shows the impact of each assumption cumulatively while Table 16 shows detailed base case results. Fully incremental base case results are given in Table 17.

When the ERG attempted to run its base case analyses probabilistically it encountered problems related to total comparator treatment costs that it didn't have time to investigate. As noted in Section 2, the company's probabilistic analyses take several hours to run. In consequence, no probabilistic results are provided.

Table 14. ERG's preferred assumptions

Assumptions	Company	ERG
Source of comparator data (Key Issue 1)	Partially adjusted MAIC	Unadjusted analysis (naïve comparison)
OS parametric distribution (Key Issue 2)	Log-normal	Log-logistic
Source of progression-based utility values (Key Issue 4)	TA242	CORRECT
Treatment-specific utility values for NIVO+IPI (Key Issue 5)	Yes	No - utility values according to progression status
Subsequent treatments (Key Issue 6)	TA405	Company's clinical expert opinion including encorafenib + cetuximab for BRAF mutated patients, and including 9 cycles of FOLFOX when patients discontinue NIVO+IPI

Abbreviations: FOLFOX, 5-FU, folinic acid and oxaliplatin; MAIC, matching adjusted indirect comparison; NIVO+IPI, nivolimumab with ipilimumab; OS, overall survival; TRI-TIP, trifluridine-tipiracil

Table 15. ERG's base case results using its preferred assumptions (cumulative)

Results per patient	NIVO+IPI (1)	TRI-TIP (2)	BSC (3)	FOLFOX (4)	FOLFIRI (5)	Incremental value			
						(1-2)	(1-3)	(1-4)	(1-5)
Company base case									
Total costs (£)	███	17,020	9,546	12,654	12,289	███	███	███	███

QALYs	■	0.689	0.477	1.029	1.287	■	■	■	■
ICER (£/QALY)						15,743	16,323	17,220	17,981

Unadjusted analysis (naïve comparison)

Total costs (£)	■	16,973	9,303	12,334	11,665	■	■	■	■
QALYs	■	0.602	0.422	0.975	0.924	■	■	■	■
ICER (£/QALY)						15,555	16,231	17,127	17,098

OS parametric distribution: log-logistic

Total costs (£)	■	■	9,303	12,334	11,665	■	■	■	■
QALYs	■	0.602	0.422	0.975	0.924	■	■	■	■
ICER (£/QALY)						15,897	16,584	17,537	17,504

Subsequent treatments based on clinical expert opinion

Total costs (£)	■	16,973	9,303	24,439	23,549	■	■	■	■
QALYs	■	0.602	0.422	0.975	0.924	■	■	■	■
ICER (£/QALY)						18,392	19,013	18,295	18,290

Source of progression-based utility values: CORRECT

Total costs (£)	■	16,973	9,303	24,439	23,549	■	■	■	■
QALYs	■	0.546	0.376	0.877	0.844	■	■	■	■
ICER (£/QALY)						20,986	21,657	20,897	20,929

Utility values according to progression status for NIVO+IPI

Total costs (£)	■	16,973	9,303	24,439	23,549	■	■	■	■
QALYs	■	0.546	0.376	0.877	0.844	■	■	■	■

Base case ICER (£/QALY)	**19,360**	**20,022**	**19,190**	**19,229**

Table 16. ERG's base case results using its preferred assumptions (pairwise)

Technologies	Total costs	Total LYs (undisc.)	Total QALYs	Inc. costs	Inc. LYs (undisc.)	Inc. QALYs	ICER (£/QALY)
Comparison A							
NIVO+IPI	■■■	■■■■	■■	-	-	-	-
TRI-TIP	16,973	0.850 (0.875)	0.546	■■	■■■	■■	19,360
Comparison B							
NIVO+IPI	■■■	■■■■	■■	-	-	-	-
BSC	9,303	0.599 (0.611)	0.376	■■	■■■	■■	20,022
Comparison C							
NIVO+IPI	■■■	■■■■	■■	-	-	-	-
FOLFOX	24,439	1.384 (1.453)	0.877	■■	■■■	■■	19,190
Comparison D							
NIVO+IPI	■■■	■■■■	■■	-	-	-	-
FOLFIRI	23,549	1.302 (1.362)	0.844	■■	■■■	■■	19,229

Table 17. ERG's base case results using its preferred assumptions (fully incremental)

Technologies	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)
BSC	£9,303	0.376	-	-	-
TRI-TIP	£16,973	0.546	£7,670	0.170	45,118
FOLFIRI	£23,549	0.844	£6,576	0.298	22,067

FOLFOX	£24,439	0.877	£890	0.033	26,970
NIVO+IPI	■■■	■■	■■■	■■	19,190

Abbreviations: BSC, best supportive care; FOLFIRI, 5-FU, folinic acid and irinotecan; FOLFOX, 5-FU, folinic acid and oxaliplatin; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYs, life years; NIVO+IPI, nivolumab with ipilimumab; QALYs, quality-adjusted life years; TRI-TIP, trifluridine-tipiracil

5   Additional figures

Figure 7. Number of patients on-treatment according to progression status over time
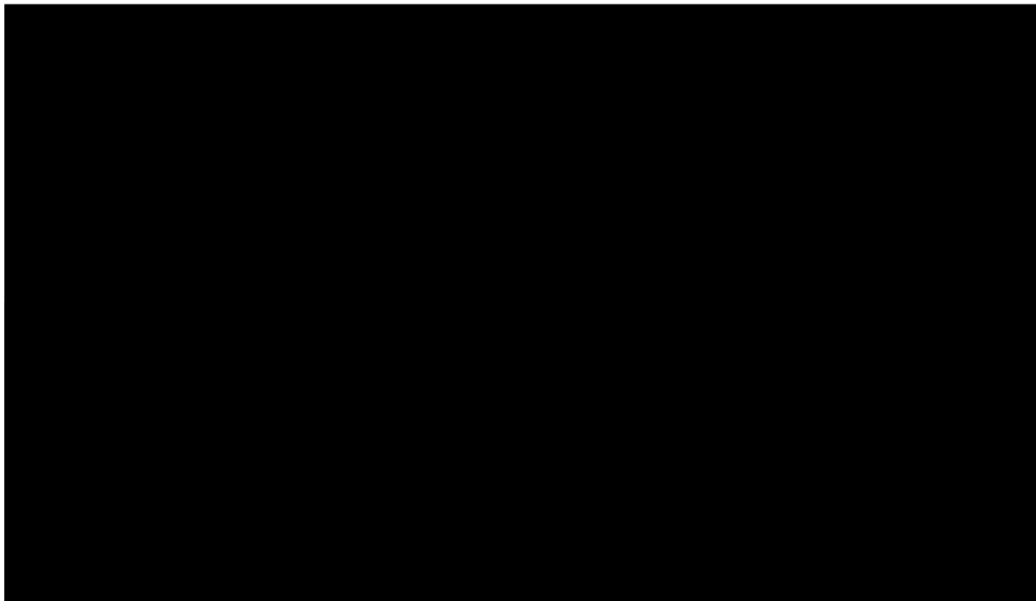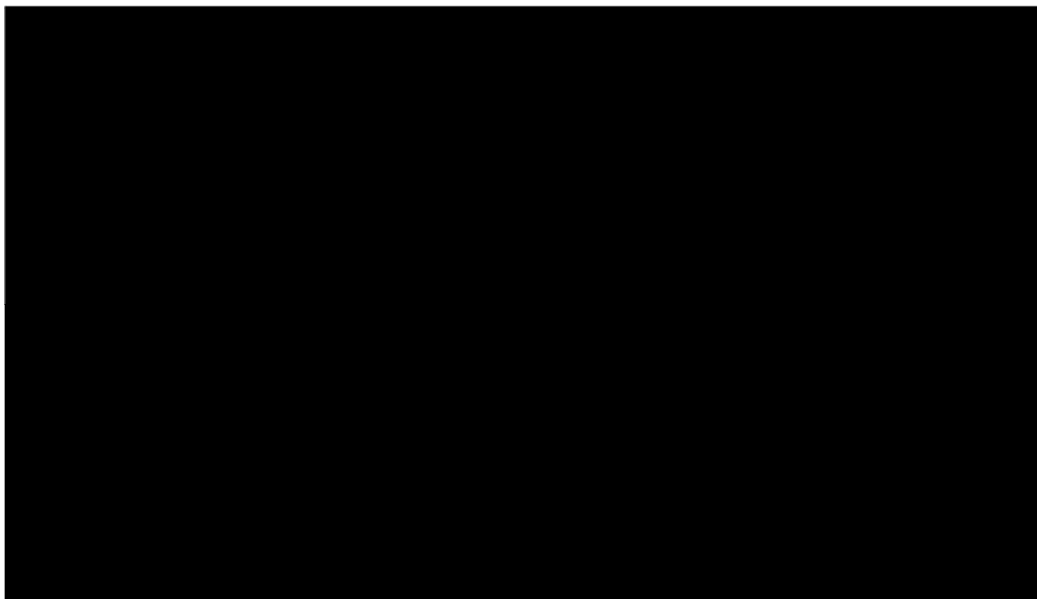

Figure 8. Number of patients on-treatment and number of patients pre-progression over time

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