NICE National Institute for Health and Care Excellence

Slides for committee only – contains ACIC

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

Lead team presentation

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Abbreviations

- **BICR -** Blinded independent central review
- **BSC -** Best supportive care
- **DBL -** Database lock
- **DCR -** Disease control rate
- **dMMR-** deficient mismatch repair
- **FOLFIRI -** Folinic acid plus fluorouracil plus irinotecan
- **FOLFOX -** Folinic acid plus fluorouracil plus oxaliplatin
- **IA -** Investigator assessed
- **ICER -** Incremental cost-effectiveness ratio
- **MAIC -** Matching-adjusted indirect comparison
- **mCRC -** Metastatic colorectal cancer
- **MSI-H -** Microsatellite instability high
- **NIVO+IPI -** Nivolumab with ipilimumab
- **ORR -** Objective response rate
- **OS -** Overall survival
- **PAS -** Patient access scheme
- **PFS -** Progression-free survival
- **QALY -** Quality adjusted life year
- **TRI-TIP -** trifluridine-tipiracil

Key Issues

Comparators and prior treatments

- How to interpret the lack of direct comparators in the single arm CheckMate 142 trial?
- Is the lack of MSI-H/dMMR specific data for the comparator treatments important?
- How important is the use of treatments not available in the NHS, such as bevacizumab in the CheckMate 142 trial and comparator trials?

Indirect treatment comparison

- Which method of indirect comparison is appropriate to compare NIVO+IPI to the comparators identified in the scope?

Stopping rule

- Would a 2-year stopping rule be used in clinical practice?

Extrapolations

- Which survival parametric distribution is more appropriate for overall survival?

Utilities

- Which utility value sets are most representative of people with mCRC?
- Would utility values vary according to treatment received?

Subsequent treatments

- Which subsequent treatment scenarios reflect subsequent treatments in clinical practice?

Metastatic colorectal cancer (mCRC)

- **Definition:** malignant tumour in large intestine which spreads to and beyond nearby lymph nodes
- **General symptoms:** change in bowel habit, abdominal discomfort, nausea, fatigue, feeling of incomplete bowel emptying
- **Survival:** determined by disease stage
  - Metastatic CRC survival rates: 1-year = 44%, 5-year = 10%
- **Treatment aims:** prolong survival, improve quality of life

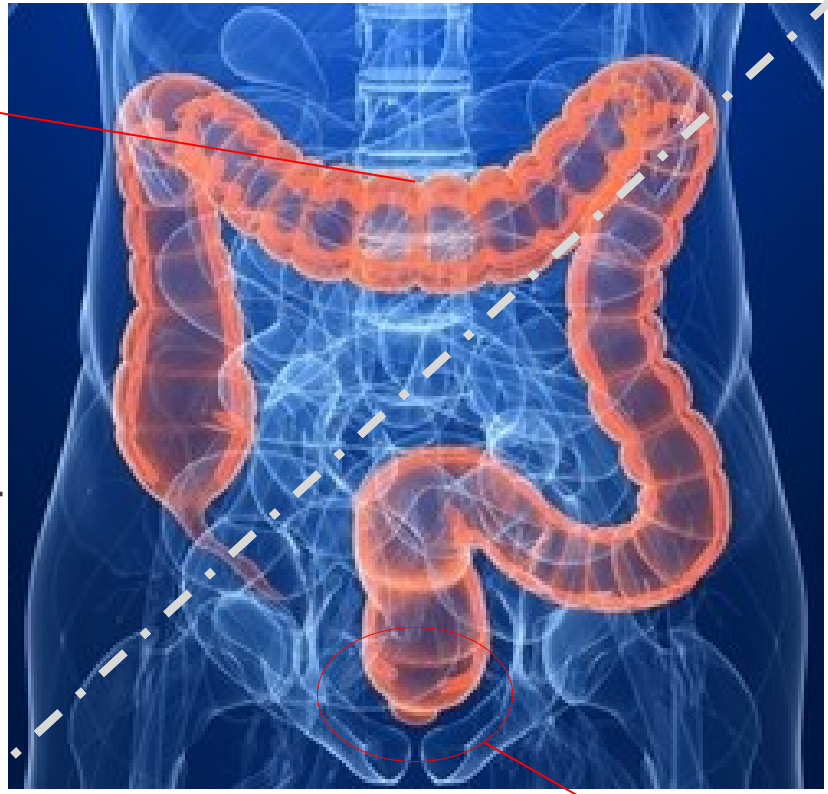
Colon: 2/3 of mCRC

R- sided tumours:

Overall survival: Worse - more likely advanced at diagnosis

Common histology: high microsatellite instability (MSI-H)/ DNA mismatch repair (dMMR)

Responds best to: immunotherapy



Rectum: 1/3 of mCRC

L- sided tumours:

Overall survival: Better

Common histology: KRAS and p53 mutant

Responds best to: adjuvant chemotherapy and targeted therapy

Source: colorectal.jpg (480×289) (qtxasset.com)

Definitions of DNA high microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR)

Resultant characteristics (phenotype)	Underlying pathology (genotype)
MSI-H • Describes cancer cells that have a greater than normal number of genetic markers called microsatellites - short, repeated, sequences of DNA • Results from MMR deficiency • Microsatellite instability most common in colorectal, other gastrointestinal, and endometrial cancer • Presence of microsatellite instability high may help plan treatment	**MMR deficiency** • MMR proteins correct single base nucleotide 'mismatches' - insertions or deletions - during DNA replication and recombination • Mismatch repair (MMR) **deficient** cells can have many mutations • MMR deficiency most common in colorectal, other gastrointestinal, and endometrial cancer • MMR deficiency may be found in inherited disorders Lynch syndrome. • Knowing if a tumour is MMR deficient may help plan treatment

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National Cancer Institute Dictionary of Cancer Terms

Characteristics of MSI-H/dMMR colorectal cancers

- **Identification:** Positive for ≥1 of:
  - **MSI-H:** Polymerase chain reaction (PCR) for microsatellite instability
  - **dMMR:** Immunohistochemical staining (IHC) for any MMR protein loss
- **Prevalence**: MSI-H/dMMR occurs in 4% of metastatic CRC
- **Outcomes vs. metastatic non-MSI-H/dMMR:** Worse mortality rates and response to standard chemotherapy
- **Treatments**: Currently no MSI-H/dMMR mCRC specific treatments at second-line

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dMMR- deficient mismatch repair; MSI-H, microsatellite instability high; mCRC- metastatic colorectal cancer

Nivolumab plus ipilimumab (Opdivo and Yervoy Bristol-Myers Squibb)

Marketing authorisation	"Adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy"
Mechanism of action	• **Nivolumab:** antibody that targets and blocks the programmed death 1 (PD-1) receptor, to promote an anti-tumour immune response • **Ipilimumab:** antibody that blocks the effects of the anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) to enhance T-cell mediated immune response to tumour cells
Administration	Intravenous infusion Nivolumab 3mg/kg with ipilimumab 1mg/kg once every 3 weeks for 4 doses followed by nivolumab 240 mg once every 2 weeks
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 Separate Patient Access Scheme (PAS) approved by Department of Health for both nivolumab and ipilimumab

Patient perspective

Unmet need for treatments for this type of colorectal cancer

Living with colorectal cancer

- Most challenging aspects are fear of recurrence, anxiety and worry that the cancer will return and unsure what a different pain or feeling in our body might mean
- Difficulty in daily activities such as outdoor activities, going to work in cold and exercise

Limited options for people with MSI-H/dMMR disease

- Current treatments are very limited for MSI-H mCRC patients with limited effectiveness
- Side effects can include severe peripheral neuropathy, frequent stomach pains and nausea as well as brain fog, memory loss and severe fatigue

NIVO + IPI advantages over current standard care

- Remarkable effectiveness - within 3 months all of my tumour had disappeared
- Minimal side-effects, NIVO+IPI is much gentler on the body than chemotherapy
- Normal life without the worry and effort of frequent hospital visits, return to work full time, travel freely and visit friends and family

"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"

Patient organisation perspective

Bowel Cancer UK

Unmet need

- Survival rates for mCRC poor, <10% survive more than five years
- Limited NHS treatment options for advanced bowel cancer, especially MSI-H disease and side effects impact quality of life both physically and emotionally
- Patients used words like '**devastating**', '**tough**', '**a battle**', **stressful**' and '**difficult**' to describe their overall experience living with advanced bowel cancer

"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"

New treatment

- Shorter and less frequent treatment, fewer hospital visits, reduced travel time and cost
- Fewer side effects and better quality of life, return to work and can experience seeing families grow and survive to see important life events (marriage, birth or graduation)

"The huge benefit to the patient's quality and extended life. The cost and time saving benefits for the NHS"

NHS metastatic colorectal cancer pathway

Currently no MSI-H/dMMR specific treatments; company positions NIVO + IPI after previous treatment as per anticipated market authorisation

KEY
- Current standard care for MSI-H /dMMR mCRC
- Recently published (non-comparator)
- Company's positioning for NIVO+IPI

During COVID19: nivolumab and pembrolizumab monotherapy available for MSI-H/dMMR

Diagnosis of metastatic colorectal cancer

Genetic testing
RAS, BRAF V600E, MSI

	All CRC types			RAS wild-type specific		MSI-H/dMMR specific
1st line	FOLFOX / mFOLFOX6	FOLFIRI	CAPOX Capecitabine **TA61**	Panitumumab with FOLFOX, mFOLFOX6 or FOLFIRI **TA439**	Cetuximab with FOLFOX, mFOLFOX6 or FOLFIRI **TA439**	Pembrolizumab monotherapy (under consideration ID1498)
2nd line plus	FOLFIRI	FOLFOX / mFOLFOX6	Single agent Irinotecan (after FOLFOX) Raltitrexed (if chemo contraindicated)	Encorafenib with cetuximab (BRAF V600F) **TA668** **(Published January 2021)**		Nivolumab with ipilimumab MSI-H/dMMR
	Trifluridine–tipiracil (after failure of other treatments) **TA405**					

Best supportive care

NICE Abbreviations: FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; mFOLFOX6, modified FOLOFOX6; TRI-TIP, trifluridine–tipiracil

Testing for high microsatellite instability or DNA mismatch repair deficiency

Genetic testing is routinely commissioned for untreated metastatic colorectal cancer

Diagnostic pathway

- Variation in uptake for high MSI or DNA MMR deficiency testing across the NHS
- Testing is routinely commissioned by NHS England. However, uptake is currently low in some places, but it is an ongoing development in the NHS
- Cancer Drug Fund lead: Testing should be offered to all newly diagnosed people before starting treatment
- NB: Nivolumab and pembrolizumab monotherapy are already available as interim treatment options during the COVID-19 pandemic for untreated colorectal cancer with high MSI or DNA MMR deficiency – increasing genetic testing uptake

Decision problem 1/2

Company excludes two comparators listed in the NICE scope

	Final scope issued by NICE	Company
Population	Adults with previously treated recurrent or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (MSI-H)	As per scope
Intervention	Nivolumab with ipilimumab	As per scope
Comparators	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)	Company excluded: • Raltitrexed • Single-agent irinotecan The ERG agrees with the company's view on the most relevant comparators

◉ ***Should raltitrexed and single-agent irinotecan be excluded as comparators?***

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FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; mCRC, metastatic colorectal cancer

Decision problem 2/2

Company addresses all outcomes in the scope

	Final scope issued by NICE	Company
Outcomes	• Progression-free survival • Overall survival • Response rate • Duration of response • Adverse effects of treatment • Health-related quality of life	Company included: Objective response rate (ORR)

Clinical effectiveness

1. *CheckMate 142: NIVO+IPI demonstrated clinically meaningful effect on efficacy endpoints*
2. *CheckMate 142 is a single arm non-comparative study; comparisons between NIVO+IPI and comparators are unanchored comparisons*
3. *CheckMate 8HW – ongoing phase IIIb randomised trial is ongoing and will provide comparative data for NIVO+IPI versus standard of care for dMMR/MSI-H mCRC but preliminary results not expected until* [redacted]

Key trial: CheckMate 142 (MSI-H/dMMR mCRC)

Location	N=119; 28 sites, five countries in Europe (Ireland, Belgium, Italy, France and Spain, not including UK) North America (USA and Canada), Australia
Control arm	None
Treatment length	Until disease progression, discontinuation because of toxicity, death, withdrawal of consent, or study end - no stopping rule
Median follow-up	2 database locks: February 2019 (XXX months follow up) XXXXXXXXX (approximately XX months follow up)
Inclusion criteria	Adults with: • histologically confirmed MSI-H/dMMR metastatic or recurrent CRC • ≥ 1L treatment(s), which must include at least (i) a fluoropyrimidine, and (ii) oxaliplatin or irinotecan • ECOG 0-1
1º endpoints	• Investigator-assessed objective response rate (composite end-point of complete and partial response)
2º endpoints	• Progression-free survival • Overall survival • Adverse affects of treatment • Disease control rate (complete and partial response + stable disease)
Quality of life	EQ-5D-3L and EORTC QLQ-C30

DBL, database lock; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; CRC, colorectal cancer, MSI-H, Microsatellite instability high

CheckMate-142 trial schema

CheckMate 142 ongoing, non-randomised - multiple arms, people are recruited according to disease stage, MSI-H status and prior treatments

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cStage : combination therapy stage; C3-C6, cohorts3-6 ,dMMR: deficient mismatch repair; mCRC: metastatic colorectal cancer; mstage, monotherapy stage

Key trial : CheckMate 142

Baseline characteristics	NIVO+ IPI (N=119)
Median age, years (range)	58 (21–88)
Gender, n (%) Male	70 (58.8)
ECOG*, n (%) 0 1	54 (45.4) 65 (54.6)
Primary tumour location, n (%) Right colon Left and sigmoid colon Transverse colon Rectum Colon, not otherwise specified	 65 (54.6) 30 (25.2) 15 (12.6) 6 (5.0) 3 (2.5)
Lynch syndrome, n Yes No Unknown	 35 (29.4) 35 (29.4) 49 (41.2)
Mutation status, n (%) Both BRAF and KRAS wildtype BRAF mutation KRAS mutation Unknown	31 (26.1) 30 (25.2) 44 (37.0) 14 (11.8)

NICE ◉ ***Are these patient characteristics generalisable to NHS clinical practice?***

Key trial: CheckMate 142 – prior treatments

Majority of people had 2 or more prior treatments

Baseline characteristics	NIVO+ IPI (N=119)
Number of prior systemic regimens, n (%)	
0 (allowed to enrol after refusing cytotoxic chemotherapy)	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)

NB: FOLFIRI, 5-FU (fluorouracil) plus irinotecan; FOLFOX, 5-FU (fluorouracil) plus oxaliplatin; FOLFIRINOX, 5-FU-Oxa-Iri

NICE ◉ ***Do these treatments represent NHS clinical practice?***

Subsequent treatment distribution

A total of [redacted] patients discontinued treatment due to disease progression – [redacted] received subsequent treatments

Subsequent treatments received by patients during CheckMate 142	N
Regorafenib	[redacted]
Investigational antineoplastic	[redacted]
FOLFIRI	[redacted]
Nivolumab / Nivolumab with ipilimumab (retreatment)	[redacted]
FOLFOX	[redacted]
Other immunotherapeutic treatments	[redacted]
Cetuximab plus irinotecan	[redacted]
Other	[redacted]

◉ Does this represent subsequent treatments expected to be used in NHS clinical practice?

FOLFIRI: 5-FU, folinic acid and irinotecan; FOLFOX: 5-FU, folinic acid and oxaliplatin

CheckMate 142- response rates

Best overall response between the date of first dose and the date of progression using RECIST 1.1 criteria (Feb 2019 data cut)

Response outcome	NIVO+IPI (N=119) BICR assessed	NIVO+IPI (N=119) Investigator assessed
Primary outcome: Objective response rate (complete and partial response), % [95% CI]	XXXXXX	XXXXXX
Secondary outcomes:		
Disease control rate (complete, partial and stable), % [95% CI]	XXXXXX	XXXXXX
Best Overall response		
Complete response, % [95% CI]	XXXXXX	XXXXXX
Partial response, % [95% CI]	XXXXXX	XXXXXX
Stable disease, %	XXX	XXX
Progressive disease, %	XXX	XXX
Unable to determine, %	XX	XX
Duration of response [95% CI]	XXXXXX	XXXXXX

BICR: blinded independent review; CI: confidence interval Source: adapted from company submission, Table 10

CheckMate 142: Progression-free survival

Median PFS [redacted] months follow-up ([redacted] data cut)

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CI: Confidence interval;; PFS: Progression-free survival

Source: Company submission, appendix 1, survival analysis, figure 4

CheckMate 142 : Overall survival

Median OS [redacted] months follow-up ([redacted] data cut)

CI: Confidence interval; OS, overall survival,

Source: Company submission, appendix 1, survival analysis, figure 18

Adverse events

- Company considered immunotherapy to have significantly lower adverse event burden than conventional therapies
- Company noted no new safety concerns were identified for nivolumab and ipilimumab

Treatment-related adverse events of special interest	Any grade n (%)	Grade 3-4 n (%)
Skin	[redacted]	[redacted]
Endocrine	[redacted]	[redacted]
Gastrointestinal	[redacted]	[redacted]
Hepatic	[redacted]	[redacted]
Pulmonary	[redacted]	[redacted]
Renal	[redacted]	[redacted]
Hypersensitivity/infusion reactions	[redacted]	[redacted]

Evidence based on the FEB 2019 data cut

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Source: Company submission, table 19

Key issues identified by the ERG

All issues identified by ERG have a minimal impact on cost-effectiveness results

	Issue	Notes	Resolved?	Impact
1	Comparator outcomes	What is the most appropriate adjustment needed for the matching-adjusted indirect comparison - naïve indirect treatment or partially adjusted?	Not resolved	
2	Stopping rule	Would a 2-year stopping rule be used in clinical practice	Resolved	
3	Survival extrapolations	Which survival parametric distribution is more appropriate for overall survival?	Partially-resolved	
4 & 5	Utility values	Which utility value sets are most representative of people with metastatic colorectal cancer?	Not resolved	
6	Subsequent treatment	Which subsequent treatment scenarios reflect subsequent treatments in clinical practice?	Partially-resolved	

 - Minimal Impact on ICER  - Reduces ICER

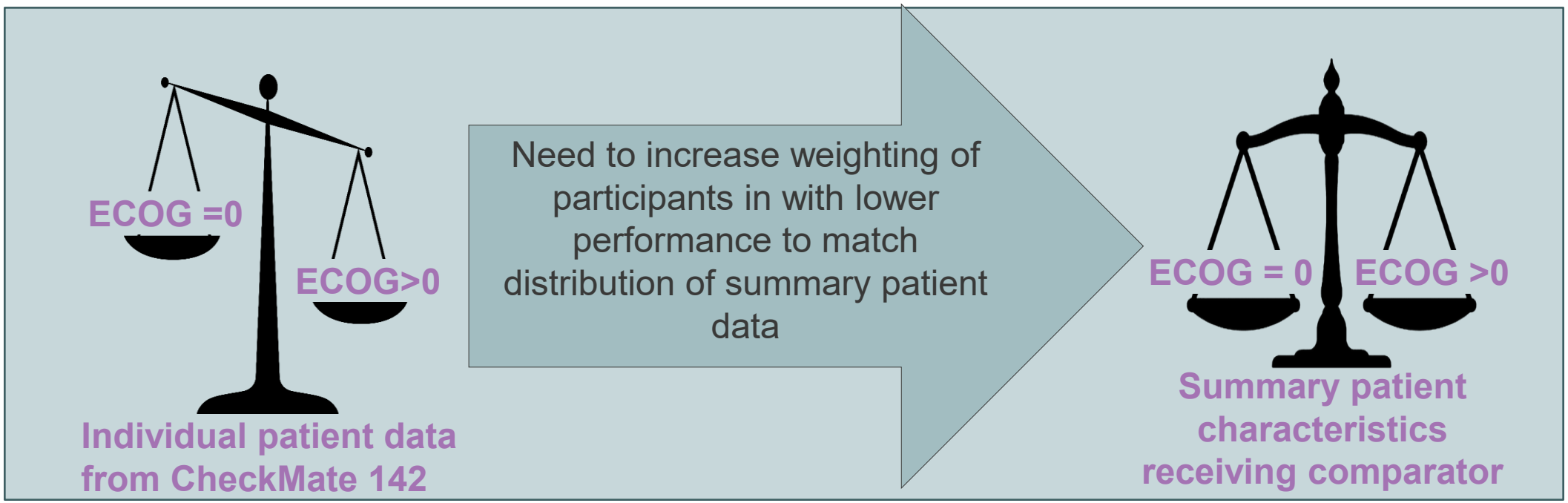
Indirect treatment comparison – company approach

- CheckMate 142 is a single arm trial – no direct comparators, systematic literature review identified relevant pre-treated populations for each comparator. Not feasible to perform meta-analysis so matching adjusted indirect comparison considered
- No MSI-H specific data were identified for the comparators and evidence from overall mCRC populations used (company considers conservative assumption because chemotherapy may be less effective in MSI-H mCRC)

Treatment	Comparator data source
FOLFOX	**CONFIRM-2 (Guglielmi 2007)** – extracted data from single arm of trial investigating the efficacy of vatalanib added to FOLFOX compared with FOLFOX alone in patients failing first-line FOLFIRI
FOLFIRI	**VELOUR (Montes 2019)** – extracted data from single arm of trial investigating efficacy of aflibercept added to FOLFIRI compared with FOLFIRI alone in patients with metastatic colorectal cancer previously treated with oxaliplatin with or without bevacizumab
TRI-TIP	**RECOURSE (Custem 2018)** – extracted both arms from EU specific (USA also available in sensitivity analysis) data from trial investigating TRI-TIP compared with best supportive care in patients with metastatic colorectal cancer refractory to standard chemotherapies
Best supportive care	

ERG comment: The ERG broadly agrees with the company's choice of individual studies

Matching adjusted indirect analysis - overview

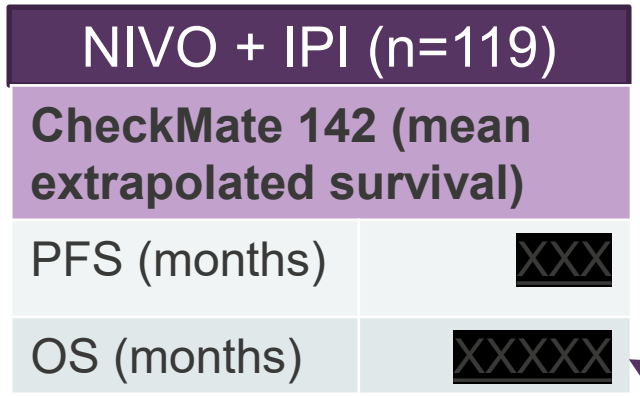


Variables considered for adjustment included:

- Demographic baseline characteristics – Age + Sex (race sometimes included)
- Predictive baseline characteristics – ECOG performance status, time from diagnosis, number of prior systemic therapies, metastases locations, primary tumour location (limited data because of differences in coding), KRAS mutation
- Other baseline characteristics – Geographic region
- Not included because of reporting limitations – Lynch Syndrome, BRAF mutation, and time to progression from most recent prior therapy regimen

Indirect comparison results – naïve vs adjusted

Matching adjustment applied to comparator arm



months	FOLFOX CONFIRM-2	FOLFIRI VELOUR	BSC RECOURSE (EU)	TRI-TIP RECOURSE (EU)
PFS - naïve	5.5	6.8	1.8	3.7
OS - naive	17.3	15.7	7.2	10.4
PFS - adjusted	4.9	10.3	2.5	5.1
OS - adjusted	18.4	23.1	8.2	11.9
Effective sample size	N=64.9	N=42.6	N=37.5	N=38.8

Source: Company submission, appendix 3

Indirect treatment comparison

Company:

- Adjusted MAIC is more relevant as it compensates for many of the observed outcomes-modifying population differences identified in CheckMate 142
- CheckMate 142 is insufficiently sized for compensation of all differences, and some subgroups have very low prevalence resulting in poor sampling of outcomes
- Discarding data where bias is reduced due to the inability to exactly match on all prognostics would not be an appropriate approach

ERG comment:

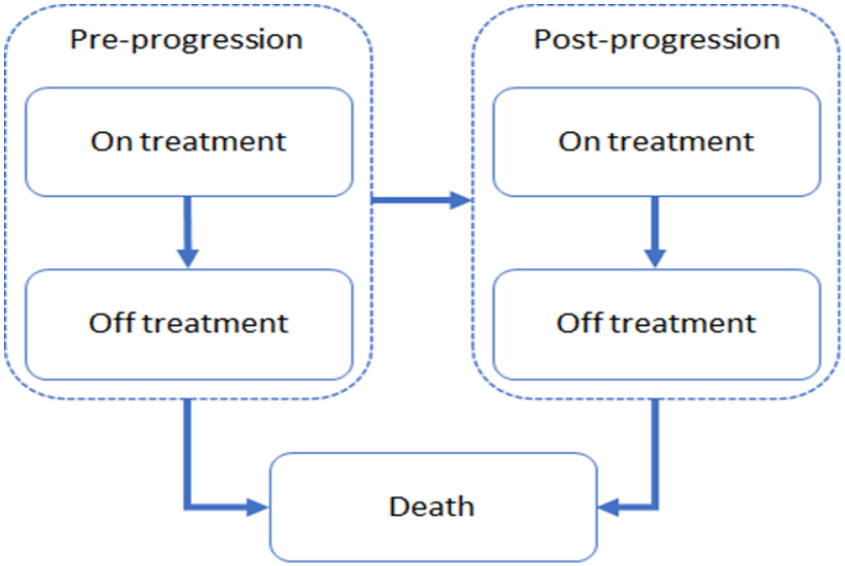
- Acknowledge adjusted MAIC may provide less biased estimates but there is no way of assessing the residual bias or any adjustments that have led to reduction in bias
- Prefer naïve comparison as it is transparent in terms of the likely biases that exist within the comparison and the analysis itself has not introduced additional bias into the comparison
- **Cost-effectiveness results** based on the naïve comparisons and adjusted comparisons **are very similar** because of the magnitude of benefit of NIVO+IPI

NICE ◉ ***Is it appropriate to use partially-adjusted or naïve comparisons?***

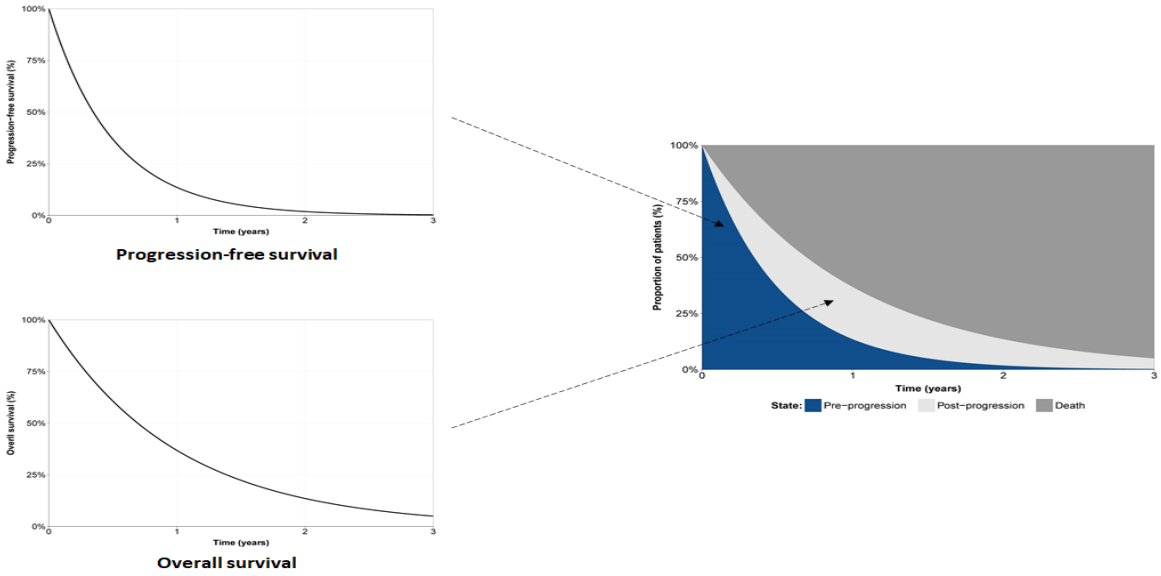
Cost effectiveness

1. *Company uses a 3-health state-partitioned survival model*
2. *Company models clinical inputs from CheckMate 142 for baseline characteristics*
3. *Pre- and post-progression survival is greater than all other comparators*

Cost effectiveness model



Three-health state partitioned survival model diagram



Overview of survival curve implementation in the model

Structure	3-state partitioned survival model
Time horizon	Lifetime (50 years)
Cycle length	Week
Stopping rule	None
Discount rate	3.5%
Perspective	NHS and PSS

How company incorporated evidence into its model

Company uses clinical data from CheckMate 142 for model inputs

Input	Evidence Source
Baseline characteristics	Population from CheckMate 142
Treatment effect	• Progression-free survival for NIVO+IPI from CheckMate 142 • Overall survival for NIVO+IPI from CheckMate 142 • Mean PFS and OS estimates for the comparators obtained from the MAIC
Adverse events	Grade 3 or higher included in the model
HRQoL data + utility values	• EQ-5D-3L from CheckMate 142 • Based on health utility index from TA242 and CheckMate 142
Costs	• Health state unit costs applied by treatment status • Generally in line with TA405
Duration of treatment	• Time on treatment from CheckMate 142 until disease progression, discontinuation because of toxicity, death, withdrawal of consent

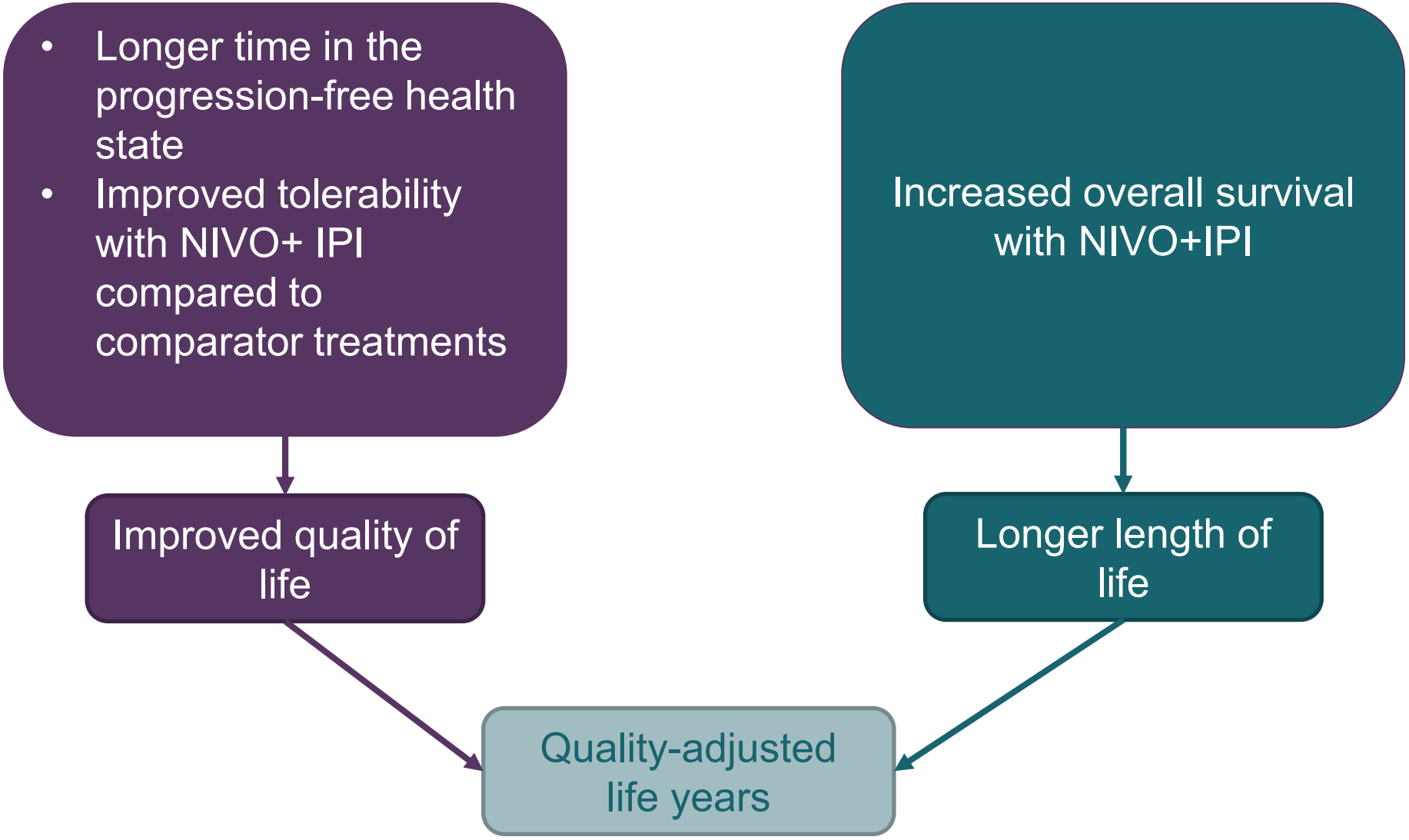
Health state unit costs – applied monthly

Type	Pre-progression	Post-progression	Source
Medical oncologist outpatient consultation	£197.70	£0.00	NHS Cost Collection 2018-19
GP home consultation	£0.00	£25.70	PSSRU 2013, inflated from 2012/13 to 2018/19 using inflation factor 1.082
Community nurse specialist visit	£0.00	£47.00	PSSRU 2019
Health home visitor	£11.67	£46.68	PSSRU 2015, inflated from 2014/15 to 2018/19 using inflation factor 1.061
District nurse visit	£0.00	£47.00	PSSRU 2019
GP surgery visit	£0.00	£39.00	PSSRU 2019

End of life costs – applied as one-off cost in the cycle prior to death	
	Source: (Round 2015) - Inflated to 2018-2019 costs
Health care	£5,194.53
Social care	£1,593.46
Total	£6,787.99

Source: Company submission, tables 44-46

Overview: how quality-adjusted life years accrue



Treatment stopping rule

 - Reduces ICER

- Company included 2-year stopping rule in its base case
- No formal stopping rule was applied in CheckMate 142
- TA439 (cetuximab and panitumumab for previously untreated mCRC) - inappropriate to implement stopping rule in mCRC (withdrawing palliative care)

Company response at technical engagement:

- Removed the 2-year stopping rule from its base-case
- Updated time on treatment data to reflect of CheckMate 142
- Updated provides a more mature time on treatment curve, which accounts for the maximum clinical benefit associated with NIVO+IPI

ERG after technical engagement:

- ERG is satisfied with 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

◉ Would a stopping rule will be used in clinical practice with NIVO+IPI?

- Minimal impact on ICER

Survival extrapolation – progression free survival

ERG and company agree on progression free survival extrapolation

ERG: Log-logistic was chosen because it has an excellent visual and statistical fit and can represent the decreasing hazard well

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Source: Adapted from CS, appendix 1, figure 11

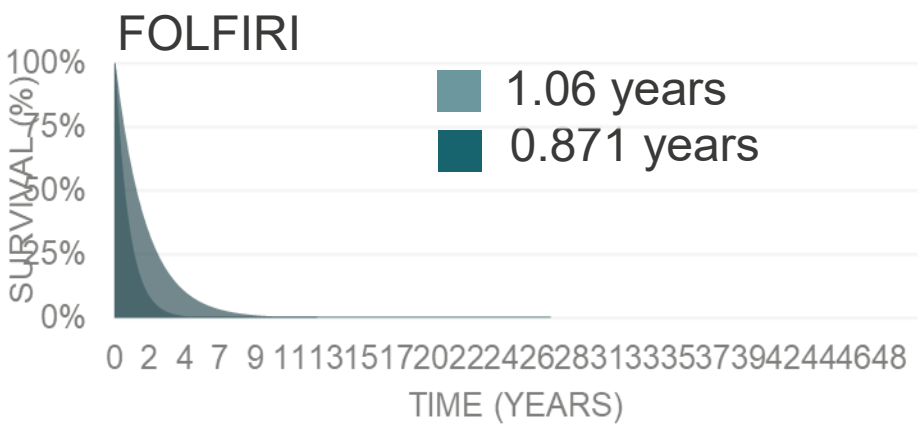
Survival extrapolation – overall survival

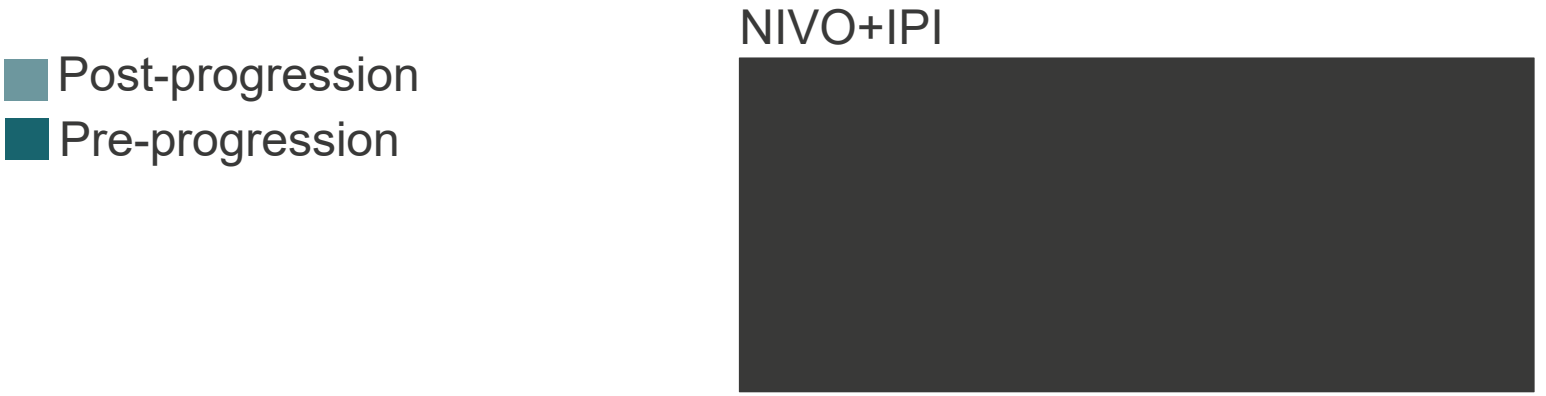
- Minimal impact on ICER

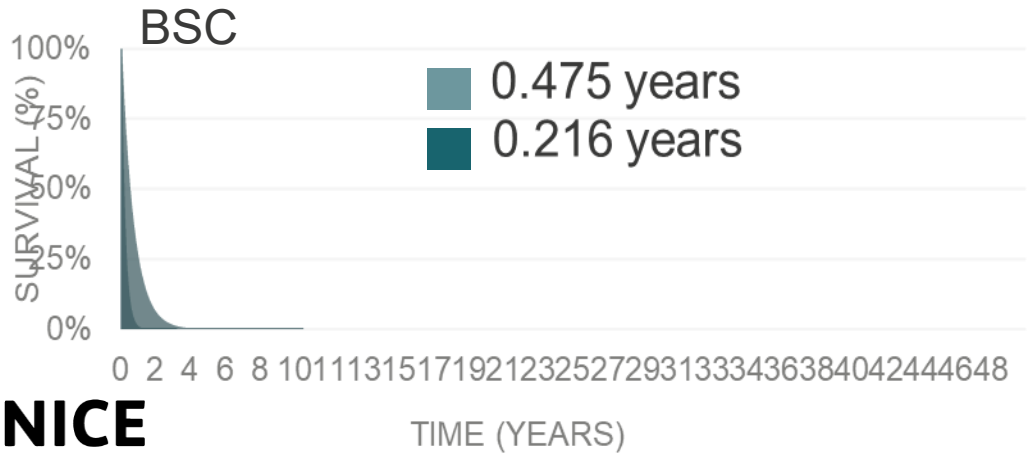
◉ *Which survival extrapolation is most appropriate for overall survival?*

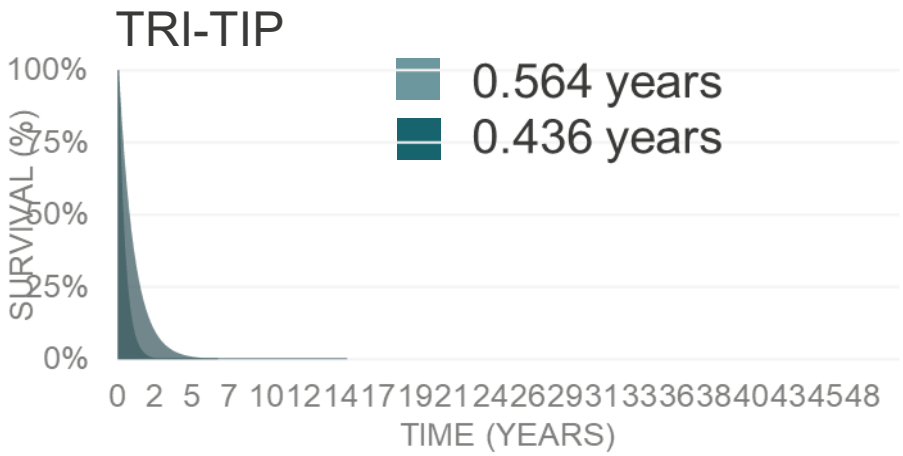
Source: Adapted from CS, appendix 1, figure 25

Modelled output - life years accrual over time









Post-progression utility values

- Minimal impact on ICER

Company: Uses utility values from TA242 (Cetuximab, bevacizumab and panitumumab for the treatment of mCRC) – consider more representative of CheckMate 142 population than CORRECT population (regorafenib for previously treated mCRC)

% of patients receiving previous systemic treatments	TA242 from Mittmann et al (2009)	CORRECT	CheckMate 142
1 line	Not reported by line 100% fluoropyrimidine 98% Oxaliplatin 96% Irinotecan	25-27 %	23%
2 lines			36%
3 (+) lines		25-28%	40%
4+ lines		47-49%	

ERG: could not validate utility values in TA242. Utility sources used health utility index rather than EQ-5D to obtain estimates which is not a reference case - maintains that the post-progression utilities are too high

Treatment	State	Utility values from TA242	Utility values from CORRECT
By progression status	Pre-progression	0.75	0.74
	Post-progression	0.69	0.59

◉ ***Which utility value sets are most representative of people with mCRC?***

Treatment-specific utilities values

- Minimal impact on ICER

Comparator	State	Utility values from TA242	Utility values from CORRECT
NIVO+IPI	On treatment	XXXXX	X
	Off treatment	0.69	-
Comparators	Pre-progression	0.75	0.74
	Post-progression	0.69	0.59

Company: Novel mechanism of action of NIVO+IPI, improved survival benefit and the reduced chemotherapy toxicities derive separate treatment-specific utility values

ERG:

Relatively small impact on cost-effectiveness results because people 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

- Considers in the absence of a randomised controlled trial with an appropriate comparator arm there is not enough evidence to justify treatment-specific utility values - consider according to progression status, from one source (CORRECT study), to be most appropriate

◉ ***Is there evidence of improved quality of life from reduced toxicity of nivolumab compared to comparators?***

Source: ERG response to TE-section 3.5, ERG response to TE- table 7

Subsequent therapy costs

- Minimal impact on ICER

- Base case assumes a one-off subsequent treatment cost upon discontinuation for all treatments of £1,621 (TA405) and additional monitoring costs for NIVO+IPI
- ERG considers this is an oversimplification because treatments would differ by arm
- Company explored three alternative scenarios to account for this difference:
  1. impact of subsequent treatments based on clinical expert opinion
  2. impact of subsequent treatments for patients who will have the BRAF mutation
  3. impact of subsequent treatment from CheckMate 142 after discontinuing NIVO+IPI

Technology	Base case	Clinical expert opinion (1)	Clinical expert opinion including encorafenib + cetuximab for BRAF mutated patients (2)	CheckMate 142 (3)
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

Subsequent therapy cost

- Minimal impact on ICER

ERG considers scenario analysis based on clinical expert opinion most appropriate

ERG has 3 key issues:

- Both scenarios based on clinical expert opinion use a median of 3-4 cycles of FOLFOX but clinical expert opinion notes up to 12 cycles could be given if patients are very fit. Expert opinion considers it would be between these values – ERG scenario explores use for 9 cycles.
- Scenario based on subsequent treatment data collected in CheckMate 142 (scenario 3), a one-off cost of £16,120 is applied to all treatment arms. ERG considers unreasonable because treatment regimens would depend on prior line of treatment
- Also for scenario 3, Checkmate 142 NIVO+IPI cohort had 119 patients, XX progressed and XX received subsequent treatment – any extrapolation is likely to be extremely unreliable
- **ERG base case**: scenario analysis based on clinical expert opinion, including encorafenib + cetuximab for BRAF mutated patients is one step closer to reflecting the subsequent treatments that will be used in clinical practice.

NICE

◉ ***What is the most appropriate subsequent treatment scenario***?

End-of-life criteria

Company and ERG agree end-of-life criteria are met

Criteria 1 – treatment is indicated for patients with a short life expectancy (normally less than 24 months)	Current standard of care for the mCRC overall population is associated with poor outcomes and company estimates of OS ranging from **6.05-12.73** months
Criteria 2 – sufficient evidence to indicate that treatment offers an extension to life (normally at least an additional 3 months) compared to current NHS treatment	Model output suggests incremental life year gain of [redacted] years

Innovation and Equality

- **Innovation**: Company considers NIVO+IPI innovative
- NIVO+IPI is a highly innovative, targeted immuno-oncology therapy with a unique mechanism of action and has significant benefits in terms of patient-relevant outcomes, including high response rates, improved survival (both PFS and OS) and a manageable safety profile
- NIVO+ IPI would change the treatment paradigm and represent a 'game-changer' in the management of previously treated dMMR/MSI-H mCRC
- 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
- **Equality issues**: None raised

◉ ***Should NIVO+IPI be considered a step-change in the treatment of MSI-H mCRC ?***

mCRC: metastatic colorectal cancer; NIVO+ IPI: nivolumab with ipilimumab; OS: overall survival; PFS: progression free survival

Key Issues

Comparators and prior treatments

- How to interpret the lack of direct comparators in the single arm CheckMate 142 trial?
- Is the lack of MSI-H/dMMR specific data for the comparator treatments important?
- How important is the use of treatments not available in the NHS, such as bevacizumab in the CheckMate 142 trial and comparator trials?

Indirect treatment comparison

- Which method of indirect comparison is appropriate to compare NIVO+IPI to the comparators identified in the scope?

Stopping rule

- Would a 2-year stopping rule be used in clinical practice?

Extrapolations

- Which survival parametric distribution is more appropriate for overall survival?

Utilities

- Which utility value sets are most representative of people with mCRC?
- Would utility values vary according to treatment received?

Subsequent treatments

- Which subsequent treatment scenarios reflect subsequent treatments in clinical practice?

Back up slides

Subsequent treatments

Company made following assumption:

- **Clinical experts:**
  - NIVO+IPI would receive a chemotherapy not previously given (FOLFOX conservatively assumed as it is the most expensive option) for 3.5 cycles
  - receiving FOLFOX or FOLFIRI would go on to receive TRI-TIP for 3 cycles
  - 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
- **BRAF mutation**
  - 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
- **CheckMate 142**
  - Treatment regimens received by more than one patient were included and time on treatment was identified from clinical trials

Assumptions: company vs ERG

Assumptions	Company	ERG
Source of comparator data	Partially adjusted MAIC	Unadjusted analysis (naïve comparison)
OS parametric distribution	Log-normal	Log-logistic
Source of progression-based utility values	TA242	CORRECT
Treatment-specific utility values for NIVO+IPI	Yes	No - utility values according to progression status
Subsequent treatments	TA405	Company's clinical expert opinion including encorafenib + cetuximab for BRAF mutated patients, and including 9 cycles of FOLFOX when patients discontinue NIVO+IPI