NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Pierre Fabre

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Royal College of Physicians and National Cancer Research Institute (NCRI) joint submission

4. **Expert personal perspectives** from:
   a. Dr Naureen Starling – clinical expert, nominated by Pierre Fabre
   b. Dr Harpreet Wasan – clinical expert, nominated by Pierre Fabre
   c. Deborah James – patient expert, nominated by Bowel Cancer UK
   d. Alexander Salkeld - patient expert, nominated by Bowel Cancer UK

5. **Evidence Review Group report** prepared by Warwick Evidence

6. **Evidence Review Group report – factual accuracy check**

7. **Technical report**

8. **Technical engagement response from company**

9. **Technical engagement responses from consultees and commentators:**
   a. Bowel Cancer UK

10. **Evidence Review Group critique of company response to technical engagement** prepared by Warwick Evidence

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

Encorafenib in dual therapy with cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Document B

Company evidence submission

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Contents

Tables and figures

Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
AIC	Akaike information criterion
AQoL	Assessment of Quality of Life
BEACON CRC	Binimetinib, Encorafenib, and Cetuximab Combined to Treat BRAF-Mutant Colorectal Cancer
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
Bini	Binimetinib
BOR	Best overall response
BRAF	B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf
BSA	Body surface area
BSC	Best supportive care
CEA	Carcinoembryonic antigen
CI	Confidence interval
CR	Complete response
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computed tomography
CSR	Clinical study report
CYP	Cytochrome P450 (2B6, 2C8, 2C9, 2C19, 3A4 refer to isoforms)
DOR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
Enco	Encorafenib
Enco+Bini	Encorafenib in combination with binimetinib
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EQ-5D-5L	EuroQoL-5 dimensions-5 levels
FACT-C	Functional Assessment of Cancer Therapy-Colon Cancer
FAS	Full Analysis Set
FOLFIRI	Folinic acid/fluorouracil/irinotecan
FOLFOX	Folinic acid/fluorouracil/oxaliplatin
HR	Hazard ratio

HRQOL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
K-M	Kaplan-Meier
KRAS	KRAS proto-oncogene, GTPase
LY	Life year
LY	Life year gained
MAPK	Mitogen-activated protein kinase
mCRC	Metastatic colorectal cancer
MEK	Mitogen-activated extracellular signal-regulated kinase
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NHS	National Health Service
NMA	Network meta-analysis
NRAS	NRAS proto-oncogene, GTPase
OAT	Organic anion transporter (1 and 3 refer to isoforms)
OATP	Organic anion transporting polypeptide (1B1 and 1B3 refer to isoforms)
ORR	Overall response rate
OR	Overall response
OS	Overall survival
PAS	Patient access scheme
PCR	Polymerase chain reaction
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PGIC	Patient global impression of change
PICC	Peripherally inserted central catheter
PPS	Post-progression state
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PSS	Personal social services
Q2W	Once every 2 weeks

QALY	Quality-adjusted life year
QD	Once daily
QoL	Quality of life
QW	Once weekly
RAF	Serine/threonine-protein kinase
RAS	RAS family of proto-oncogenes, GTPases
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SLI	Safety lead-in
StD	Stable disease
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TTD	Time to treatment discontinuation
TSD	Technical Support Document
TTR	Time to response
ULN	Upper limit of normal
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

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

B.1.1 Decision problem

Statement on company decision problem in relation to regulatory status

- This submission covers the technology's full (anticipated) marketing authorisation for the proposed indication for the treatment of adults with previously treated B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf (BRAF) V600E mutation-positive metastatic colorectal cancer (mCRC), which includes the following regimen:
  - Double combination of encorafenib with cetuximab (from this point referred to as Enco with cetuximab).
- In October 2019 Pierre Fabre originally submitted a regulatory dossier to the European Medicines Agency (EMA) for a marketing authorisation for the triple combination of encorafenib and binimetinib in combination with cetuximab (from this point referred to as Enco+Bini with cetuximab), based on the "Binimetinib, Encorafenib, and Cetuximab Combined to Treat BRAF-Mutant Colorectal Cancer" (BEACON CRC) interim analysis (data cut-off February 2019).
- In light of the recent availability of the most mature dataset from the BEACON CRC trial (15th August 2019) and feedback from the EMA, Pierre Fabre believes that the double combination offers the most favourable benefit-risk profile and are now pursuing an application for the double combination of Enco with cetuximab only.
- In this context, the company decision problem now focuses solely on the double combination of Enco with cetuximab.
- Clinical trial information relating to Enco+Bini with cetuximab is only included in this submission for completeness, where providing evidence from the BEACON CRC trial. No economic analyses have been submitted for the triple combination.

Table 1 summarises the decision problem addressed by the company submission.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously treated BRAF V600E mutation-positive mCRC.	As per scope.	N/A.
Intervention	• Encorafenib with cetuximab (from this point referred to as Enco with cetuximab). • Encorafenib with binimetinib and cetuximab (from this point referred to as Enco+Bini with cetuximab).	Enco with cetuximab.	In line with the decision by Pierre Fabre to only pursue marketing authorisation for the double combination of Enco with cetuximab. The triple combination of Enco+Bini with cetuximab is no longer relevant to decision making in England and has been omitted from the company decision problem.
Comparator(s)	• Folinic acid plus fluorouracil plus irinotecan (FOLFIRI). • Irinotecan. • Trifluridine-tipiracil (only after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable). • BSC.	• Folinic acid plus fluorouracil plus irinotecan (FOLFIRI). • Trifluridine-tipiracil (only after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable).	BSC • BSC refers to supportive care to manage the symptoms and complications of the condition, when patients have exhausted all active treatment options (due to failure, lack of tolerability or contraindicated). The anticipated use of Enco with cetuximab would be earlier in the treatment pathway, where active treatments are still available (i.e. FOLFIRI or trifluridine-tipiracil). • Therefore, BSC is not considered to be an appropriate comparator and will not be considered in the company decision problem. Irinotecan • The use of single-agent irinotecan as per the marketing authorisation is not considered a relevant comparator after first-line treatment. Data based on patient-level information collected by the NHS[†] shows use of single-agent irinotecan accounted for only 1.8% of therapies used at second-line by patients with mCRC (1). Responses from 11 practicing oncologists who were consulted on treatment usage for BRAF-mutant mCRC also showed that single-agent irinotecan is

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			rarely used as a second-line agent (n=1/11) (2) and additional expert input[a] sought for this submission further supports this. • Therefore, single-agent irinotecan is not considered to be an appropriate comparator and will not be considered in the company decision problem.
Outcomes	• The outcome measures to be considered include: – OS. – PFS. – Response rates. – Adverse effects of treatment. – HRQoL.	As per scope	N/A.

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; BSC, best supportive care; HRQoL, Health-related quality of life; mCRC, metastatic colorectal cancer; N/A, not applicable; OS, overall survival; PFS, progression-free survival.
† Data for this is based on patient-level information collected by the NHS. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to this data was facilitated by the Simulacrum (1).

[a] Two research activities were conducted to elicit information and test assumptions for the submission. Overall these two exercises elicited responses from three NHS consultant oncologists practicing in England: 1. Advisory board attended by two NHS consultant oncologists practicing in England, and three health economists; 2. Face to face meeting followed by telephone follow-up with an NHS consultant oncologist practicing in England.

B.1.2 Description of the technology being appraised

Encorafenib, marketed as BRAFTOVI® is currently licensed, in combination with binimetinib (MEKTOVI®), to treat adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, and received positive technology appraisal (TA) guidance (TA562) from NICE in February 2019[b].

This submission covers the double combination of Enco with cetuximab for patients with BRAF V600E-mutant mCRC, who have received prior systemic therapy. The Enco with cetuximab regimen is the first and only therapy to be investigated in a Phase 3 trial and marketing authorisation sought, specifically for patients with BRAF V600E-mutant mCRC.

The draft summary of product characteristics (SmPC) for encorafenib is presented in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	UK approved names: Encorafenib Brand names: BRAFTOVI
Mechanism of action	• The MAPK signalling pathway (also known as the RAS/RAF/MEK/ERK pathway) regulates cellular growth, proliferation, differentiation and survival (3). BRAF (along with RAS) is a serine/threonine protein kinase that plays an important role in the EGFR-mediated MAPK pathway. BRAF (especially V600E) mutations disrupt kinase function, leading to the constitutive activation of MEK and ERK, enhancing cell proliferation and prolonged cell survival (3), and thus growth of the tumour. • **Encorafenib** is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor, which supresses the RAF/MEK/ERK pathway in colorectal cancer cells expressing V600E mutations. A slow dissociation half-life of over 30 hours results in prolonged pERK inhibition. • **In combination with cetuximab** – Activation of EGFR has been identified as one of the mechanisms of resistance of BRAF-mutant CRC to RAF inhibitors. Therefore, in the setting of BRAF-mutant CRC, EGFR-mediated MAPK pathway activation presents with an additional therapeutic opportunity to combine a RAF inhibitor with an EGFR inhibitor, such as cetuximab.
Marketing authorisation/CE mark status	• Encorafenib, marketed as BRAFTOVI® is currently licensed, in combination with binimetinib (MEKTOVI®), to treat adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, and received positive TA guidance from NICE in February 2019 (TA562). • For the new indication of previously treated BRAF V600E-mutant mCRC: – An initial regulatory submission was made to the EMA on 15th October 2019.

[b] https://www.nice.org.uk/guidance/ta562

	– In light of the availability of the most mature dataset from the BEACON CRC trial (15th August 2019) and feedback from the EMA, Pierre Fabre are now pursuing an application for the double combination only. – CHMP positive opinion is anticipated on 28th May 2020, with a planned launch in early August 2020.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Draft indication covered in this submission** • Encorafenib in combination with cetuximab, for the treatment of adult patients with mCRC with a BRAF V600E mutation, who have received prior systemic therapy. ***Existing indication*** • *Encorafenib in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.*
Method of administration and dosage	• **Encorafenib:** The recommended dose is 300 mg (four 75 mg capsules) QD, when used in combination with cetuximab. • **Cetuximab:** – Prior to the first infusion patients must receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions (4). – The SmPC recommendation on dosing is an initial dose of 400 mg per m^2 body surface area, followed by 250 mg/m^2 for all subsequent doses given once weekly (4). – In contrast, CDF guidance from NHS England, which reflects current clinical practice in England, recommends a maintenance dosing schedule of 500 mg/m^2 given every 2 weeks (5).
Additional tests or investigations	**BRAF mutation testing:** Before taking encorafenib, patients must have mCRC with BRAF V600E mutation confirmed by a validated test. In practice, Pierre Fabre understands this is already happening in the majority of treatment centres (6). NICE Guideline (NG151) "Colorectal cancer" published on 29th January 2020, recommends testing for BRAF V600E (and RAS) mutations in all people with mCRC who are suitable for systemic anti-cancer treatment (7). BRAF mutation testing is currently commissioned as part of a "multi-target NGS panel - small variant (KRAS, NRAS, BRAF)", in patients with CRC who may be eligible for anti-EGFR therapy and/or in whom BRAF status is required as per the NICE diagnostic guidance for molecular testing for Lynch syndrome (7-9). Furthermore, Pierre Fabre understands that in the NHS England financial year 2021, seven genomic laboratory hubs will commence panel testing with all patients having the BRAF V600E test at metastatic disease stage.
List price and average cost of a course of treatment	**Encorafenib:** • List price £1,400 (PAS [redacted]) per pack of 42 x 75 mg capsules (10). • List price £622.22 (PAS [redacted]) per pack of 28 x 50 mg capsules (10). **Cetuximab:** • List price £890.50 per 500 mg/100 mL (10).

	• A commercial access arrangement is applicable, but the discount is unknown to Pierre Fabre; see below. Prices are exclusive of VAT. **Enco with cetuximab regimen:** • The total cost per calendar month of treatment (Mean 30.42 days): – for encorafenib would be £4,056 at list price ([redacted] with PAS) (based on 300 mg QD) and – for cetuximab would be £3,482 at list price (maintenance dose of 500 mg/m^2 every 2 weeks based on mean BSA of 1.79 mg/m^2 from the BEACON CRC trial and dose rounded according to dose banding tables; see Section B.3.5.1.1.1 for further details of calculation). Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity.
Patient access scheme (if applicable)	For encorafenib there is a simple PAS agreed between Pierre Fabre and NHS England; the PAS price is incorporated within this submission. Cetuximab, marketed by Merck Serono is subject to a confidential commercial arrangement, which the NHSE have confirmed is applicable to combination treatment with Enco in the mCRC setting. Pierre Fabre are not party to the discount applicable. As such, only the cetuximab list price is considered in this submission.

Abbreviations: ATP, adenosine triphosphate; BID, twice daily; BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; CDF, Cancer Drugs Fund; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; (m)CRC, (metastatic) colorectal cancer; MEK, mitogen-activated extracellular signal-regulated kinase; NHS, National Health Service; PAS, patient access scheme; QD, once daily; RAF, Serine/threonine-protein kinase.

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

B.1.3.1 Overview

Colorectal cancer (CRC) is a malignant tumour arising from the lining of the large intestine (colon and rectum). mCRC refers to disease that has spread (metastasised) beyond the large intestine and nearby lymph nodes and represents an advanced form of the disease. This type of cancer often first spreads to the liver, but metastases may also occur in other parts of the body including the lungs and bones (11).

The cause of CRC is unknown. Risk factors for CRC include being overweight or obesity, smoking, drinking too much alcohol, eating processed meat, or eating too little fibre (12). Incidence is strongly related to age, with 44% of new cases in people aged 75 and over (13).

Symptoms of CRC include bleeding from the rectum, blood in the faeces, changes in bowel habit, weight loss, and anaemia. Obstruction of the bowel can also occur resulting in cramping, bloating, constipation and vomiting (14).

CRC is the fourth most common cancer in the UK and accounted for 12% of all new cancer cases in 2016 (15); there were 34,952 new cases in England in 2016 (15) and around 22% were diagnosed at the metastatic stage (16). In addition, around 50% of patients diagnosed with CRC will progress to develop metastases (17). CRC is the second most common cause of cancer death in the UK, and accounted for 10% of all cancer deaths in 2017 (18); there were 13,566 deaths from CRC in England in 2017 (18).

One-, five- and ten-year survival in CRC overall is around 76, 59 and 57%, respectively (19), and survival rates have improved, with 10-year survival rates more than doubling in the last 40 years in the UK (22% to 57%) (20). However, England has a lower average survival rate for CRC than other European countries (21). Moreover, mCRC is particularly difficult to treat due to the advanced nature of the condition and only one in ten (10.3%) people with mCRC survive for five years or more, compared with nine out of ten diagnosed at the earliest stage of the disease (22).

Approximately 8% of people in the UK have tumours with a mutation in a cell signalling protein called BRAF (23, 24), and the vast majority of these mutations are specifically V600E mutations (97–100% (23-25)). Mutations in the BRAF protein alter its function, leading to sustained activation of the mitogen-activated protein kinase (MAPK) signalling pathway, which ultimately leads to enhanced cell proliferation and longer cell survival (3). Importantly, the presence of the BRAF mutation identifies a subset of patients with a significantly poorer prognosis and risk of disease recurrence than those with wild-type BRAF/RAS family of proto-oncogenes, GTPases (RAS) mCRC (26). BRAF mutation more than doubles the risk of mortality (Hazard ratio [HR] for death vs BRAF wild-type 2.24; 95% confidence interval (CI): 1.82, 2.83) (27), while median survival rates with current treatments are substantially lower (e.g. 4.2 months in BRAF-mutant mCRC vs 15.5 months in RAS/BRAF wild-type for folinic acid/fluorouracil/irinotecan (FOLFIRI) at second-line (28)).

B.1.3.2 Clinical pathway of care

The overall aims of treatment for mCRC are to control the symptoms, maintain (or improve) quality of life (QoL), slow the spread of the tumours, and prolong survival. mCRC

treatment can involve a combination of surgery (to resect the primary tumour or the metastases), radiotherapy (to destroy and shrink the cancer, and relieve symptoms), cytotoxic chemotherapy (to destroy cancer cells, relieve symptoms and improve QoL), targeted therapy (to shrink or slow cancer cell growth) and supportive care (29, 30).

NICE has made a number of TA recommendations for mCRC treatments (31-37) and has also published clinical guidelines for CRC; NICE Clinical Guideline 131 "Colorectal cancer: diagnosis and management" in December 2014 (38), and recently updated and replaced by NICE Guideline 151 "Colorectal cancer" on January 29th 2020 (7).

None of these specifically cover treatments for BRAF-mutant populations.

B.1.3.2.1 Treatment options in non-BRAF-mutant mCRC

Up until recently and based on **NICE Clinical Guideline 131**, for patients with advanced and mCRC, NICE recommended consideration of one of the following combination chemotherapy sequences unless contra-indicated (38):

- FOLFOX (Folinic acid/fluorouracil/oxaliplatin) as first-line treatment then FOLFIRI (Folinic acid/fluorouracil/irinotecan) as second-line treatment, or
- FOLFOX as first-line treatment then single-agent irinotecan as second-line treatment, or
- XELOX (capecitabine/oxaliplatin) as first-line treatment then FOLFIRI as second-line treatment.

The recent update to the colorectal cancer clinical guideline (published as **NICE Guideline 151,** 29th January 2020 (7)), has seen this algorithm removed, with NICE now directing clinicians to the NICE Pathway on CRC (39) which only provides recommendations for treatments that have been appraised by NICE via the TA process. FOLFIRI, FOLFOX and single-agent irinotecan have not been appraised through NICE's TA process. Trifluridine-tipiracil has been appraised through NICE's TA process and is the only regimen recommended as a subsequent or alternative therapy (after first-line therapy) in the NICE Pathway.

A number of treatments are restricted by line of therapy or by the drug combinations within which they have to be given, based on NICE TA recommendations. These include the following:

- Trifluridine-tipiracil is recommended according to **NICE TA405**, within its marketing authorisation as an option for treating mCRC in adults who have had previous treatment with available therapies, including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, vascular endothelial growth factor (VEGF) inhibitors (e.g. bevacizumab) and epidermal growth factor receptor (EGFR) inhibitors (e.g. cetuximab), or when these therapies are not suitable (31).
- The biological targeted EGFR inhibitor therapies, cetuximab or panitumumab are recommended only for the first-line treatment of EGFR-expressing, RAS wild-type mCRC in adults when taken in combination with FOLFOX or FOLFIRI (**NICE TA118/TA242/TA439**) (33, 35, 37).
- Oral therapy with capecitabine is recommended as an option only for the first-line treatment of mCRC, as per **NICE TA61** (32).

Other biological therapies (aflibercept and bevacizumab) are not recommended (alone or in combination) by NICE for the treatment of mCRC (**NICE TA118, TA212, TA242** and **TA307** (33-36)).

B.1.3.2.2 Treatment options in BRAF-mutant mCRC

The reality for patients with BRAF-mutant mCRC is that there are currently no treatments available which are specifically directed at the BRAF-mutation, and because CRC mutations in BRAF and those of another signalling protein, RAS, are mutually exclusive (25), patients are typically treated with regimens available for RAS wild-type mCRC (40). Expert opinion (see Table 1 footnote “a”) suggests that patients would generally receive chemotherapy with FOLFOX at first-line, followed by FOLFIRI at second-line, and trifluridine-tipiracil at third-line. Alternatively, some patients may receive all chemotherapy options at first-line, i.e. FOLFOXIRI (Folinic acid/ fluorouracil/ oxaliplatin/ irinotecan), in which case second-line options would then be limited to trifluridine-tipiracil. Other treatments, such as EGFR inhibitors (e.g. cetuximab) may also be used as first-line

options in combination with chemotherapy (e.g. FOLFOX with cetuximab) (41), in line with NICE TA439 (37).

FOLFIRI is considered as the main second-line treatment option based on clinical expert opinion (see Table 1 footnote "a"). Data based on patient-level information collected by the National Health Service (NHS)[c] shows that single-agent irinotecan is rarely used accounting for only 1.8% of therapies used as a second-line agent by patients with mCRC (1). Responses from 11 practicing oncologists who were consulted on treatment usage for BRAF-mutant mCRC also showed that single-agent irinotecan is rarely used as a second-line agent (n=1/11) (2) and additional expert input (see Table 1 footnote "a") sought for this submission further supports this. It should also be noted that, as stated previously, single-agent irinotecan has not been appraised through NICE's TA process.

If all active treatment options have been exhausted (due to failure, lack of tolerability or contraindicated), patients would be managed with supportive care to manage the symptoms and complications of the condition.

B.1.3.2.3 Place in therapy

It is anticipated that Enco with cetuximab would enter the existing clinical pathway following first-line chemotherapy:

- as an alternative option to FOLFIRI (in patients previously treated with FOLFOX at first-line) or
- as an alternative option to trifluridine-tipiracil (in patients previously treated with FOLFIRI at second-line) or
- as an alternative option to trifluridine-tipiracil (in patients previously treated with FOLFOXIRI at first-line).

As described above, single-agent irinotecan is not considered to be an appropriate comparator and as such is not listed in the existing pathway.

[c] Data for this is based on patient-level information collected by the NHS. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to this data was facilitated by the Simulacrum.

Given that best supportive care (BSC) would generally be confined to later lines of therapy, when all active treatments have been exhausted, BSC is also not considered to be an appropriate comparator.

B.1.3.3 Unmet need

BRAF-mutant mCRC represents an extremely challenging disease state to treat, with the prognosis being far worse than with non-BRAF-mutant disease – risk of mortality more than doubled versus BRAF wild-type (27) – and treatment choices being limited to those used in wild-type RAS disease. Effectiveness data supporting the use of treatments in BRAF-mutant populations is limited (See Section B.2.1 for systematic review of interventions for BRAF-mutant mCRC) and the only targeted treatments currently available are the biological therapies, such as cetuximab and panitumumab (EGFR inhibitors), and bevacizumab (VEGF inhibitor), which are not indicated specifically in a BRAF-mutant population and not recommended by NICE beyond first-line therapy (33-37).[d]

In the absence of treatments specifically for patients with colorectal tumours with BRAF V600E mutations, standard second-line therapies currently provide limited benefit with an overall survival (OS) of approximately 4 to 6 months (28, 42-44). These rates are substantially lower than observed in BRAF wild-type disease (e.g. median OS 4.2 months in BRAF-mutant mCRC vs 15.5 months in RAS/BRAF wild-type for FOLFIRI at second-line (28)).

A cytotoxic chemotherapy-free treatment option which specifically targets the BRAF V600E mutation and can result in significantly improved clinical outcomes, including progression-free survival (PFS) and OS is required to support improved patient care.

Enco with cetuximab for patients with BRAF-mutant mCRC

- The Enco with cetuximab regimen provides a step change in the treatment of BRAF-mutant mCRC, being the first and only therapy to show demonstrable improvements in OS, PFS, and health-related quality of life (HRQoL), and a favourable safety profile in this specific patient group versus standard of care treatments in a Phase 3 clinical trial specifically designed for this population.

[d] All NICE recommendations for these biological therapies resulted in being “not recommended” for mCRC; these appraisals do not cover BRAF-mutated disease.

- There is currently no agent specifically indicated for patients with BRAF V600E-mutant mCRC. Patients with BRAF V600E-mutant mCRC patients have been treated to date with standard of care regimens for RAS wild-type mCRC, and there is only limited evidence of treatment benefit for these therapies in this patient population
- Given the very poor prognosis for patients with BRAF V600E-mutant mCRC and the complete lack of a BRAF-mutant specific treatment, there is a clear and high unmet need in this patient population.
- A positive NICE recommendation for Enco with cetuximab will provide patients and clinicians with a first-in-class oral[e] and chemotherapy-free targeted therapy for BRAF V600E-mutant mCRC patients who have received prior systemic therapy, that can lead to improved survival and HRQoL.

B.1.4 Equality considerations

Use of Enco with cetuximab is not expected to raise any equality issues.

[e] Encorafenib is taken orally; cetuximab is taken as an IV infusion.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Two systematic reviews were conducted – one for RCTs and one for non-randomised trials/observational studies – to identify all relevant clinical data assessing the clinical effectiveness and safety of treatments, including Enco with cetuximab and relevant comparators for BRAF V600E-mutant mCRC.

The systematic reviews had a broad scope covering all lines of therapy across mCRC, irrespective of the genetic status; studies in 2nd/3rd-line therapy and in populations that were solely BRAF-mutant mCRC or reported on a subgroup of patients with BRAF-mutant mCRC were prioritised to inform evidence synthesis; evidence identified was used to determine the feasibility of conducting network meta-analyses to derive relative effectiveness estimates for Enco with cetuximab versus relevant comparators (See Section B.2.10 for further details).

An overview of the methodology, search results and list of included studies and list of excluded studies at full paper review is provided in Appendix D, Section D.1.1 for the randomised controlled trial (RCT) search and D.1.2 for the non-RCT search.

B.2.2 List of relevant clinical effectiveness evidence

Enco with cetuximab has been studied in a single Phase 3 RCT – BEACON CRC – in a population with BRAF V600E-mutant mCRC, a summary of which is provided in Table 3.

A Phase 1b/2 study of Enco with cetuximab in BRAF-mutant mCRC (45) was also identified by the RCT systematic review and was assessed for inclusion in network meta-analysis; however given that it is a Phase 1b/2 study and only assesses encorafenib at a lower dose than recommended in the licence for BRAF V600E-mutant mCRC (200 mg once daily [QD] vs 300 mg QD) the study was not considered to provide any additional clinical effectiveness evidence of relevance and has not been considered further.

Table 3: Clinical effectiveness evidence

Study	**BEACON CRC (Study ARRAY-818-302)**
Study design	A global, multicentre, randomised, open-label, three-arm, active controlled Phase 3 study.
Population	Patients with BRAF V600E-mutant mCRC whose disease had progressed after one or two prior regimens in the metastatic setting.

Study	BEACON CRC (Study ARRAY-818-302)				
Intervention(s)	• Enco 300 mg QD with cetuximab IV QW (N=220). • Enco 300 mg QD + Bini 45 mg BID with cetuximab IV QW (N=224).				
Comparator(s)	• Investigator's choice of either (N=221): – Irinotecan IV Q2W/cetuximab IV QW or – FOLFIRI (Folinic acid IV Q2W/Fluorouracil Q2W/irinotecan IV Q2W)/cetuximab IV QW.				
Indicate if trial supports application for marketing authorisation	Yes	***X***	**Indicate if trial used in the economic model**	Yes	***X***
	No			No	
Rationale for use/non-use in the model	Used in cost-effectiveness model: The pivotal, and only Phase 3 study supporting the EMA regulatory submission for Enco with cetuximab, providing comparative evidence versus standard of care at the time the trial was conducted.				
Reported outcomes specified in the decision problem†	• **OS** • **PFS** • Response rate (ORR) • **AEs** • **HRQoL** (EORTC QLQ-C30, FACT-C, **EQ-5D-5L**, and PGIC)				
All other reported outcomes	• DOR, TTR				

Abbreviations: AE, adverse event; BID, twice daily; BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; DOR, duration of response; EMA, European Medicines Agency; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQoL-5 dimensions-5 levels; FACT-C, Functional Assessment of Cancer Therapy-Colon Cancer; HRQoL, Health-related quality of life; IV, intravenous; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PGIC, Patient global impression of change; QW, once weekly; Q2W, Once every 2 weeks; TTR, time to response.
†Outcomes marked in bold are used in the model.

B.2.3 Overview of the BEACON CRC trial

- BEACON CRC is the first and only Phase 3 RCT designed specifically for patients with BRAF V600E-mutant mCRC, whose disease had progressed after one or two prior regimens in the metastatic setting.
- The trial is a global, multicentre, randomised, open-label, active controlled trial evaluating targeted therapy with encorafenib in combination with cetuximab (Enco with cetuximab; N=220), compared with investigator's choice of chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab (control arm; N=221).
- Although NICE guidance in non-BRAF-mutant populations restricts the use of cetuximab to first-line therapy in England (see Section B.1.3.2.1), the choice of

FOLFIRI or irinotecan in combination with cetuximab as the control arm represented the most frequently used therapeutic options among second- or third-line therapies at the time of study initiation in global terms, consistent with European and US guidelines (European Society for Medical Oncology and National Comprehensive Cancer Network) (17, 46).

- BEACON CRC also assessed the triple combination of encorafenib and binimetinib with cetuximab (Enco+Bini with cetuximab; N=224) and the primary endpoints of the study were designed to test OS and overall response rate (ORR) for this combination versus control. However, with the favourable results observed for the double combination, marketing authorisation for the triple combination is not being sought at this time.
- Comparisons of the Enco with cetuximab arm with the control arm were assessed as secondary endpoints, and these analyses are presented as key evidence in this submission.
- Analyses are available at two data cut-offs (February 2019 and August 2019); the August data cut is presented as the key evidence for this submission, representing the final and most mature analysis available.[f]
- In the BEACON CRC trial, the double combination of Enco with cetuximab consistently showed statistically and clinically significant improvements in OS, PFS and ORR, with a favourable and manageable tolerability profile and sustained HRQoL, compared with FOLFIRI or irinotecan with cetuximab.
- Compared with the control arm at the August 2019 data cut-off, Enco with cetuximab resulted in:
  - A 39% reduction in the risk of death equating to 3.4 additional months of survival fulfilling NICE end-of-life criteria – Median OS 9.30 months vs 5.88 months; HR: 0.61; 95% CI: 0.48, 0.77; one-sided p<0.0001.
  - A 56% reduction in the risk of disease progression or death – Median PFS 4.27 months vs 1.54 months; HR: 0.44; 95% CI: 0.35, 0.55; one-sided p<0.0001.

[f] Efficacy and safety results for the final analysis (August 2019 final data cut-off; includes ORR for all randomised patients, representing an additional 364 patients to the interim ORR analysis, and 6 months additional follow-up) were consistent with the interim analysis (February 2019 data cut-off) published by Kopetz et al (47).

- A significantly higher rate of complete or partial response (ORR) – 19.5% vs 1.8%; one-sided p<0.0001.

- HRQoL findings across a number of disease-specific and generic patient-reported tools were consistent with the observation of clinical benefit and favourable toxicity and tolerability of Enco with cetuximab compared with control.
  - Enco with cetuximab substantially delayed deterioration in HRQoL by approximately [redacted] months, as measured by median time to definitive 10% deterioration in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30) domain scores, Functional Assessment of Cancer Therapy-Colon Cancer (FACT-C) domain scores and EuroQoL-5 dimensions-5 levels (EQ-5D-5L) visual analogue scale (VAS) and utility index scores.

B.2.4 Summary of trial methodology: BEACON CRC (ARRAY-818-302)

B.2.4.1 Sources

Data from two data cut-off dates are available and presented, as listed below:

- **11th February 2019 data cut-off**
  - Clinical study report (CSR) 12th September 2019 (48).
  - Kopetz NEJM 2019, supplementary appendix and protocol (Phase 3) (47).
  - Kopetz Gastrointestinal Cancers Symposium 2020 (49).
  - Van Cutsem 2019 (Safety lead-in [SLI]) (40).
- **15th August 2019 data cut-off**
  - CSR efficacy addendum 19th December 2019 (44).
  - August update safety tables and figures 20th November 2019 (50).
  - August update patient-reported outcome (PRO) tables and figures 3rd February 2020 (51).
  - Kopetz Gastrointestinal Cancers Symposium 2020 (49).

B.2.4.2 Location

Patients were randomised at [redacted] clinical sites in [redacted] countries: [redacted] sites in Europe, [redacted] sites in North America and [redacted] sites in selected countries from the rest of the world. Patients (n=[redacted]) from [redacted] UK sites were randomised.

B.2.4.3 Study objective

The objective of BEACON CRC was to evaluate whether treatment with the combination of Enco with cetuximab with or without the MEK inhibitor binimetinib would result in longer OS than standard of care therapy in patients with BRAF V600E–mutant mCRC whose disease had progressed after one or two prior regimens in the metastatic setting.

B.2.4.4 Trial design

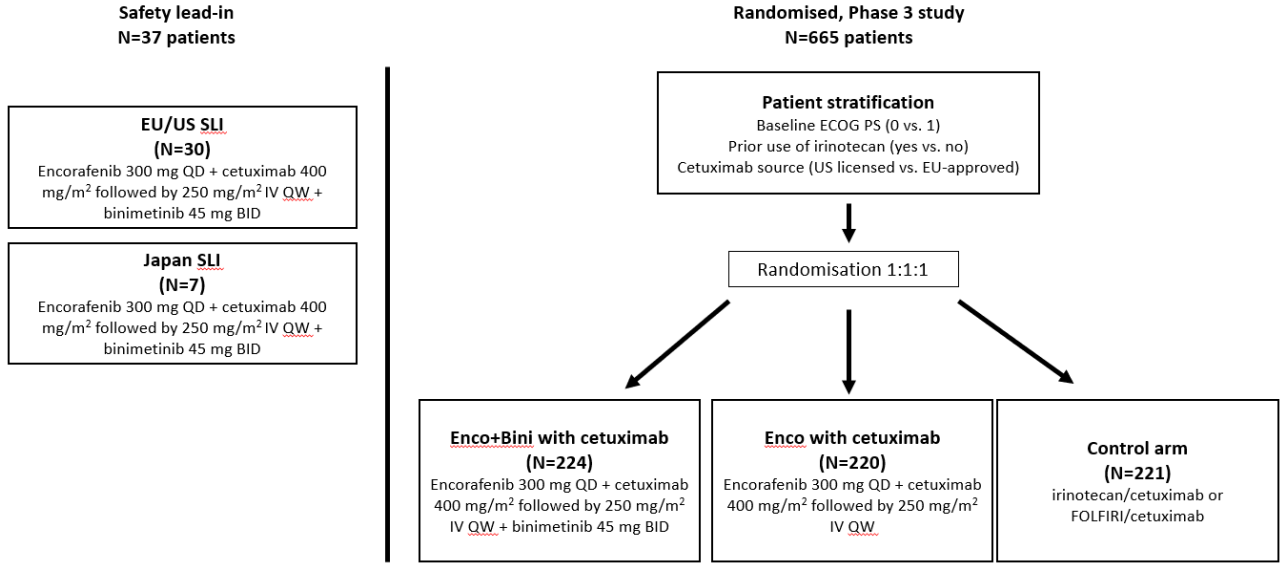
B.2.4.4.1 Overview

The BEACON CRC study is a global, multicentre, randomised, open-label, three-arm, active controlled Phase 3 study in patients with BRAF V600E-mCRC, whose disease had progressed after one or two prior regimens in the metastatic setting and provides the pivotal evidence supporting the anticipated licensed indication for Enco with cetuximab in mCRC.[g]

[g] The study also investigated the triple combination of Enco+Bini with cetuximab, however these results are not relevant to decision-making as this regimen will not be licensed. Key efficacy results for this regimen, which include the primary endpoints of the study (OS and ORR for Enco+Bini with cetuximab versus control) and the secondary PFS endpoint are provided in Appendix L for completeness; other secondary efficacy endpoints and safety results for the Enco+Bini with cetuximab regimen are not provided.

The study consisted of two main periods: a SLI period followed by the Phase 3 randomised period (Figure 1).

Figure 1: Study schematic



Abbreviations: BID, twice daily; ECOG, Eastern Cooperative Oncology Group Performance Status; FOLFIRI, folinic acid/fluorouracil/irinotecan; IV, intravenous; QD, once daily; QW, once weekly.

B.2.4.4.2 Safety lead-in period

Prior to initiation of the randomised Phase 3 portion of the study, the study was initiated with a SLI cohort, which evaluated the safety and tolerability of Enco+Bini with cetuximab in 30 patients at sites in the EU and US. A separate cohort of patients in Japan (Japanese SLI; N=7) were evaluated for the safety and tolerability of Enco+Bini with cetuximab while the randomised Phase 3 study was ongoing in other regions, but before randomisation occurred in Japan.

The SLI is not discussed further in this submission.

B.2.4.4.3 Randomised period and follow-up

BEACON CRC was designed to randomise approximately 615 patients (665 patients were actually randomised) at a 1:1:1 ratio to the following arms:

- Enco with cetuximab
- Enco+Bini with cetuximab
- Control arm comprising investigator's choice of either:
  - Irinotecan with cetuximab, or
  - FOLFIRI with cetuximab

Posology details are provided in Section B.2.4.7.

Randomisation was stratified according to the following factors:

- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs 1)
- Prior use of irinotecan (yes vs no)
- Cetuximab source (US licensed vs EU-approved)

The number of third-line patients (those who had received two prior regimens) was limited to 35% of the total randomised Phase 3 population (as per protocol), after which only patients with one prior regimen were to be randomised. Patients with two prior regimens who had entered screening at the time that the limit had been reached were to be permitted to continue into the study if they were otherwise determined to be eligible.

The treatment phase consisted of 28-day treatment cycles which continued until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death or discontinuation from study treatment for any other reason (e.g. lost to follow-up).

An end of treatment visit was to be performed for all patients, even those who discontinued prematurely (within 14 days after the last dose of study treatment).

Regardless of the reason for study treatment discontinuation, all patients were to have a safety follow-up visit approximately 30 days after the last dose of study treatment, or prior to initiation of subsequent anticancer therapy, whichever occurred first.

After the safety follow-up visit, patients were to be followed for survival status and disease progression.

B.2.4.4.4 Method of randomisation

Each patient was assigned a unique patient number via the interactive web response system (IWRS) upon enrolment for molecular pre-screening or study screening. Randomisation was used to ensure that treatment assignment was unbiased; prior to dosing, all patients who fulfilled all inclusion/exclusion criteria were randomised via IWRS to one of the treatment arms. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a computerised central randomisation list using an IWRS.

B.2.4.4.5 Blinding

As this was an open-label study, investigators and patients knew the study treatment assigned. To minimise bias, the Sponsor and their designee trial team, and the independent review committee were blinded to patient treatment assignment. The randomisation schedule was created and managed by a third-party vendor and treatments were assigned according to a central randomisation list using the IWRS. A limited number of study personnel were not blinded to individual treatment assignments for the purposes of study conduct but did not have access to unblinded aggregate summaries of data. These steps were to remain in place until a database lock supporting a CSR occurred. Sponsor personnel were to remain blinded to aggregate OS results until the Enco+Bini with cetuximab arm vs control arm OS endpoint exceeded the superiority boundary, or the study was stopped for futility.

B.2.4.5 Study period

- **Date of randomisation in Phase 3:** May 2017 to January 2019
- **Date of data cut-off (Initial analysis):** 11th February 2019
- **Date of 2nd data cut-off:** 15th August 2019

B.2.4.6 Eligibility criteria for participants

Patients must have had a BRAF V600E mutation identified to be eligible for the study; as such patients had to meet eligibility criteria to go through molecular pre-screening for determination of V600E mutation status, before then being assessed for eligibility for study participation. Full eligibility criteria for both molecular pre-screening and for study participation are provided in Appendix L.

Patients were permitted to undergo molecular tumour pre-screening with the central laboratory BRAF mutation assay at any time prior to screening as long as they met all the molecular pre-screening eligibility criteria. Tumour samples that were previously determined to be wild-type BRAF by local assessment were permitted to be submitted to the central laboratory.

To participate in the study, patients had to be at least 18 years of age with histologically- or cytologically-confirmed BRAF V600E-mutant mCRC as determined by a local or Sponsor-designated central laboratory. A patient's disease had to have progressed after one or two

prior regimens in the metastatic setting. Patients were eligible to receive cetuximab per locally approved label with regard to tumour RAS status.

Patients were also to have evidence of measurable or evaluable non-measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an ECOG PS of 0–1 and adequate bone marrow, organ and cardiac function, including left ventricular ejection fraction ≥50% by cardiac imaging and QTcF ≤480 msec.

B.2.4.7 Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)

Intervention arms

- Encorafenib QD with cetuximab intravenous (IV) once weekly (QW) (N=220)
- Encorafenib QD + binimetinib twice daily (BID) with cetuximab IV QW (N=224)

Control arm

- Investigator's choice of either (N=221):
  - FOLFIRI (Folinic acid IV once every 2 weeks [Q2W]/Fluorouracil Q2W/irinotecan IV Q2W) with cetuximab IV QW or
  - Irinotecan IV Q2W with cetuximab IV QW

Encorafenib and binimetinib

Encorafenib and binimetinib were administered at doses of 300 mg QD and 45 mg BID, respectively.

Encorafenib was provided as 75 mg capsules for QD oral administration. Binimetinib was provided as 15 mg film-coated tablets for BID oral administration, and were to be taken approximately 12 ± 2 hours apart at home. Patients were instructed to take encorafenib and binimetinib with a large glass of water (approximately 250 mL) daily at approximately the same time each morning. Both encorafenib and binimetinib were to be taken without regard to food. On the days when blood was collected at the clinic, morning doses of encorafenib and binimetinib were to be taken at the clinic. Doses of encorafenib that were missed for any reason were to be taken up to 12 hours prior to the next dose; missed doses of binimetinib were not to be made up either later in the day or at the end of the dosing period. Patients were instructed to swallow the capsules/tablets whole and not to chew or crush them.

Cetuximab

Cetuximab was administered as a QW IV infusion (Days 1, 8, 15 and 22 [±3 days)] of every 28-day cycle): 400 mg/m^2 initial dose (120-min infusion on Cycle 1 Day 1), then 250 mg/m^2 (60-min infusion) thereafter.

Infusion rate was not to exceed 10 mg/min. Premedication for routine cetuximab infusions was to be administered as described following institutional standards, 30 minutes prior to infusion. Oral dosing of encorafenib and binimetinib was to be taken 30 minutes prior to cetuximab, and cetuximab administration was to be completed 1 hour prior to the start of FOLFIRI or irinotecan infusion for control arm patients.

Irinotecan

Irinotecan was administered as a Q2W IV infusion (Days 1 and 15 [±3 days] of every 28-day cycle) at a 180 mg/m^2 dose (90-minute infusion).

Folinic acid

Folinic acid was administered as a Q2W IV infusion (Days 1 and 15 [±3 days] of every 28-day cycle) at a 400 mg/m^2 dose (120-minute infusion).

Fluorouracil

Fluorouracil was administered as an initial 400 mg/m^2 IV dose followed by 1,200 mg/m^2/day IV infusion for 2 days [total 2,400 mg/m^2 over 46–48 hours] given Q2W (Days 1 and 15 [±3 days] of every 28-day cycle).

All IV drugs were to be administered at the study site.

B.2.4.8 Permitted and disallowed concomitant medications

B.2.4.8.1 Permitted therapy

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient was permitted, unless otherwise specified.

B.2.4.8.2 Permitted concomitant therapy requiring caution and/or action

The following therapies were permitted but required caution and/or action:

- Drugs that are sensitive substrates of cytochrome (CYP) 2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and uridine diphosphate-glucuronosyltransferase 1A1 or those substrates that have a narrow therapeutic index.

- Moderate inhibitors of CYP3A4 and strong inhibitors of CYP2C19 when co-administered with Enco.
- Strong inhibitors of uridine diphosphate-glucuronosyltransferase 1A1 when co administered with binimetinib.
- Drugs that are known to inhibit or induce P-glycoprotein or breast cancer-resistance protein.
- Drugs that are known to be sensitive or narrow therapeutic index substrates of breast cancer-resistance protein, P-glycoprotein, Organic anion transporter (OAT) 1, OAT3, organic cation transporter 2, organic anion transporting polypeptide (OATP) 1B1 and OATP1B3.
- Hematopoietic growth factors (e.g. erythropoietin, granulocyte colony stimulating factor and granulocyte-macrophage colony stimulating factor) were not to be administered prior to first dose of study treatment. After irinotecan or FOLFIRI treatment, if a dose delay was required due to any grade of neutropenia, prophylactic use of granulocyte colony stimulating factor and granulocyte-macrophage colony stimulating factor prior to the next administration of FOLFIRI was permitted at the investigator's discretion. Use of these drugs was to be reserved for patients who required this therapy as per the labelling of these agents or as dictated by local practice.
- Drugs with a known, conditional or possible risk to prolong the QT interval and/or induce Torsades de Pointes.
- Anticholinergics in patients with potential contraindications (e.g. obstructive uropathy, glaucoma and tachycardia).

B.2.4.8.3 Prohibited concomitant therapy

The following therapies were prohibited during the study:

- Other anticancer agents (e.g. cytotoxic chemotherapy, small molecule targeted agents, biological agents, immune response modifiers or hormonal therapy)
- Investigational drugs and devices
- Radiation therapy (not including palliative radiotherapy at focal sites that covered ≤10% of the bone marrow reserve)
- Herbal preparations/medications
- Concomitant strong systemic CYP3A4 inhibitors.

- Combination anticholinergic medications containing barbiturates or other agents in patients receiving irinotecan.

B.2.4.9 Primary outcomes

B.2.4.9.1 OS

The original sole primary end point was OS in the Enco+Bini with cetuximab arm as compared with the control group. An interim analysis of OS (Initial analysis at data cut-off 11th February 2019) was added in an attempt to expeditiously assess efficacy.

Definition: OS was defined as the time from randomisation to death due to any cause.

Assessments: After the 30-day Safety Follow-up Visit, all patients, were followed for survival status every 3 months, or more frequently as needed, until withdrawal of consent, patient was lost to follow-up, death or end of study.

B.2.4.9.2 ORR

The protocol was amended to include an additional primary end point of the ORR by RECIST version 1.1 in the Enco+Bini with cetuximab arm as compared with the control group, as assessed by blinded independent central review (BICR).

Definition: ORR was defined as the number of patients achieving a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the total number of patients in that treatment arm (see Appendix L for definitions of BOR, CR etc).

Assessments: Tumour response was evaluated locally by the investigator and retrospectively by BICR (blinded to treatment assignment) according to RECIST version 1.1. Any lesion that had been previously treated with loco-regional therapies (e.g. radiotherapy, ablation etc.) was to be considered as a non-target lesion, unless it had shown clear progression since the initiation of study treatment, in which case, it was permitted to be considered as a target lesion.

Tumour assessments were performed every 6 weeks (±7 days) from the date of randomisation until disease progression for the first 24 weeks of treatment, then every 12 weeks (±7 days) thereafter until disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, patient was lost to follow-up, death or end of study, regardless of whether trial treatment was discontinued.

Tumour assessments performed at screening/baseline and at post-screening/baseline visits included:

- Computed tomography (CT) (preferred) with IV contrast (if not contraindicated) or magnetic resonance imaging (MRI), of the chest, abdomen and pelvis.
- Brain CT with IV contrast or MRI, for patients with history of asymptomatic brain metastases. Post-screening/baseline, brain CT or MRI scan only if brain metastases were documented at baseline.
- Whole body bone scan imaging, if clinically indicated (i.e., if bone metastases were suspected or known at baseline), using an imaging method per local standard of care. Post-screening/baseline, whole body bone scans did not need to be repeated, unless clinically indicated; however, localised CT, MRI or X-rays of all skeletal lesions identified on the screening/baseline bone scan, if not visible on the chest, abdomen and pelvis CT/MRI, were to be performed.

All CRs and PRs were confirmed by a second assessment ≥4 weeks later. Local characterisation of CRs required normalisation of carcinoembryonic antigen (CEA) in patients with elevated levels at baseline. Patients with an overall response (OR) of stable disease (StD) or better per RECIST version 1.1 at ≥5 weeks after the first dose who did not satisfy the definition of a BOR of CR or PR, were assigned a BOR of StD.

B.2.4.10 Other outcomes

Key secondary efficacy endpoint

- OS: Enco with cetuximab vs control

Other secondary endpoints

All remaining analyses of ORR, PFS, duration of response (DOR) and time to response (TTR) (all by BICR and by investigator) and OS were conducted for Enco with cetuximab vs control, for Enco+Bini with cetuximab vs control, and for Enco+Bini with cetuximab vs Enco with cetuximab.

ORR was defined as described in Section B.2.4.9.2. PFS, DOR and TTR were defined as follows:

- PFS: defined as the time from randomisation to the earliest documented date of disease progression, per RECIST version 1.1 and as determined by Investigator, or death due to any cause.

- DOR: defined as the time from first radiographic evidence of response to the earliest documented progressed disease (PD) or death and is calculated for responders only.
- TTR: defined as the time from date of randomisation to date of first radiographic evidence of response (CR or PR).

PROs were also assessed including EORTC QLQ-C30, FACT-C, EQ-5D-5L and patient global impression of change (PGIC).

B.2.4.11 Baseline characteristics and demographics

Patient characteristics at Phase 3 study baseline are summarised in Table 4. Overall, the treatment arms were mostly balanced with respect to baseline demographic and disease and tumour characteristics.

The majority of patients were White (82.7%), with a [redacted] patients in the control arm [redacted] compared with the Enco with cetuximab and Enco+Bini with cetuximab arms [redacted]). Overall, slightly more females (52.8%) than males were enrolled. Most patients were [redacted]%), with a median age of 61 for all patients.

ECOG PS as per the electronic case report form was largely evenly divided between 0 (50.5%) and 1 (48.9%), with four patients (0.6%) with ECOG PS of 2 (all were in the Enco with cetuximab arm and were ECOG PS 1 at randomisation).

An inclusion criterion for the study was the presence of a BRAF V600E mutation at baseline that was determined either by local or central analysis. Most patients were positive for a BRAF V600E mutation at baseline, as determined by central analysis ([redacted]%). Of [redacted] patients who had a BRAF mutation per local result, [redacted] patients had no mutation detected by central analysis and [redacted] patients had a central assay outcome that did not confirm the local positive result (i.e., the result was indeterminate, there was no neoplastic cell in tissue, or the result was missing).

A majority of patients overall (56.8%) had had complete resection of the primary tumour. The mean and median number of organs involved at baseline was [redacted] and [redacted], respectively. The liver was the most common sight of metastases, affecting 61.1% of patients, with lung, lymph nodes and peritoneum/omentum also being affected.

The percentage of patients who had progressed after one or two prior systemic regimens for metastatic disease was similar across the three treatment arms, with more patients overall who received one prior systemic regimen (65.7%) than two prior systemic regimens (34.0%). Approximately [redacted] of all patients ([redacted]%) received prior irinotecan and [redacted] patients ([redacted]%) received prior oxaliplatin. A [redacted]% Enco with cetuximab arm, [redacted]% Enco+Bini with cetuximab arm, [redacted]% control arm) [redacted].

Table 4: Baseline characteristics and demographics – FAS[§]

	Enco+Bini with cetuximab N=224	Enco with cetuximab N=220	Control N=221
Sex, n (%)			
Male	105 (46.9)	115 (52.3)	94 (42.5)
Female	119 (53.1)	105 (47.7)	127 (57.5)
Age (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	62	61	60
Min, max	26, 85	30, 91	27, 91
Race, n (%)			
Asian	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Black/African American	[redacted]	[redacted]	[redacted]
Other[†]	[redacted]	[redacted]	[redacted]
Not reported due to confidentiality reasons	[redacted]	[redacted]	[redacted]
ECOG PS at baseline, n (%)[‡]			
0	116 (51.8)	112 (50.9)	108 (48.9)
1	108 (48.2)	104 (47.3)	113 (51.1)
2	0 (0.0)	4 (1.8)[§]	0 (0.0)
Number of prior systemic regimens for metastatic disease, n (%)			
1	146 (65.2)	146 (66.4)	145 (65.6)
2	77 (34.4)	74 (33.6)	75 (33.9)
>2	1 (0.4)	0 (0.0)	1 (0.5)
Prior irinotecan, n (%)	[redacted]	[redacted]	[redacted]
Prior oxaliplatin, n (%)	[redacted]	[redacted]	[redacted]
Primary tumour location, n (%)			
Left colon, including rectum	79 (35.3)	83 (37.7)	68 (30.8)
Right colon	126 (56.3)	110 (50.0)	119 (53.8)
Left and right colon	[redacted]	[redacted]	[redacted]

	Enco+Bini with cetuximab N=224	Enco with cetuximab N=220	Control N=221
Unknown	[redacted]	[redacted]	[redacted]
Primary tumour removed, n (%)			
Completely resected	133 (59.4)	123 (55.9)	122 (55.2)
Partially resected/unresected	91 (40.6)	97 (44.1)	99 (44.8)
Number of organs involved			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Number of organs involved, n (%)			
≤2	114 (50.9)	117 (53.2)	123 (55.7)
≥3	110 (49.1)	103 (46.8)	98 (44.3)
Sites of metastases, n (%)			
Liver	144 (64.3)	134 (60.9)	128 (57.9)
Lung	[redacted]	[redacted]	[redacted]
Lymph Node	[redacted]	[redacted]	[redacted]
Peritoneum/Omentum	[redacted]	[redacted]	[redacted]
MSI Status (PCR), n (%)			
Abnormal high	22 (9.8)	19 (8.6)	12 (5.4)
Abnormal low	[redacted]	[redacted]	[redacted]
Normal	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
CEA at baseline, n (%)			
>5 µg/L	179 (79.9)	153 (69.5)	178 (80.5)
≤5 µg/L	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
CRP at baseline, n (%)			
>0.01 g/L	95 (42.4)	79 (35.9)	90 (40.7)
≤0.01 g/L	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Abbreviations: CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAS, Full Analysis Set; MSI, microsatellite instability; PCR, polymerase chain reaction; SD, standard deviation.
† Other includes categories of American Indian/Alaska Native and Other; ‡ ECOG PS as per eCRF at baseline and not per IWRS at randomisation; § All four patients were ECOG PS 1 by the time of randomisation per the IWRS; § no formal comparisons between treatment groups were performed.
Source: CSR (48); Kopetz 2019 (47).

B.2.5 Statistical analysis and definition of study groups: BEACON CRC

B.2.5.1 Populations analysed

The following populations were considered in the study:

- **Full Analysis Set (FAS):** the FAS included all randomised Phase 3 patients. Patients were analysed according to the treatment arm and stratum they were assigned to at randomisation.
- **Per-Protocol Set:** included all Phase 3 patients from the FAS without any major protocol deviations (or other criteria that could largely impact efficacy results) and who received at least 1 dose of study drug. The deviations that led to patient exclusion included:
  - No histologically or cytologically confirmed mCRC
  - Not positive for BRAF V600E mutation per central assessment
  - Prior treatment with any serine/threonine-protein kinase (RAF) inhibitor, MEK inhibitor, cetuximab, panitumumab or other EGFR inhibitor
  - Baseline ECOG PS ≥3
  - Study treatment received different from treatment assigned by randomisation
- **Phase 3 Response Efficacy Set:** consisted of the first 330 patients randomised and any additional patients randomised on the same day as the 330th randomised patient (n=331). Corresponds to initial analysis data cut-off 11th February 2019.
- **Safety Set:** included all patients who received at least one dose of study drug and had at least one post-treatment assessment, which may have included death. Patients who received the wrong study treatment (i.e. different from the one assigned by randomisation) for only a part of the treatment period were analysed according to the randomised treatment. If patients had received a wrong study treatment during the whole treatment period, they would have been analysed according to the actual treatment received.

The planned interim analysis of the primary endpoint of ORR for Enco+Bini with cetuximab vs control was analysed using the Phase 3 Response Efficacy Set. Unless otherwise stated, other efficacy analyses for Phase 3 patients were performed using the FAS.

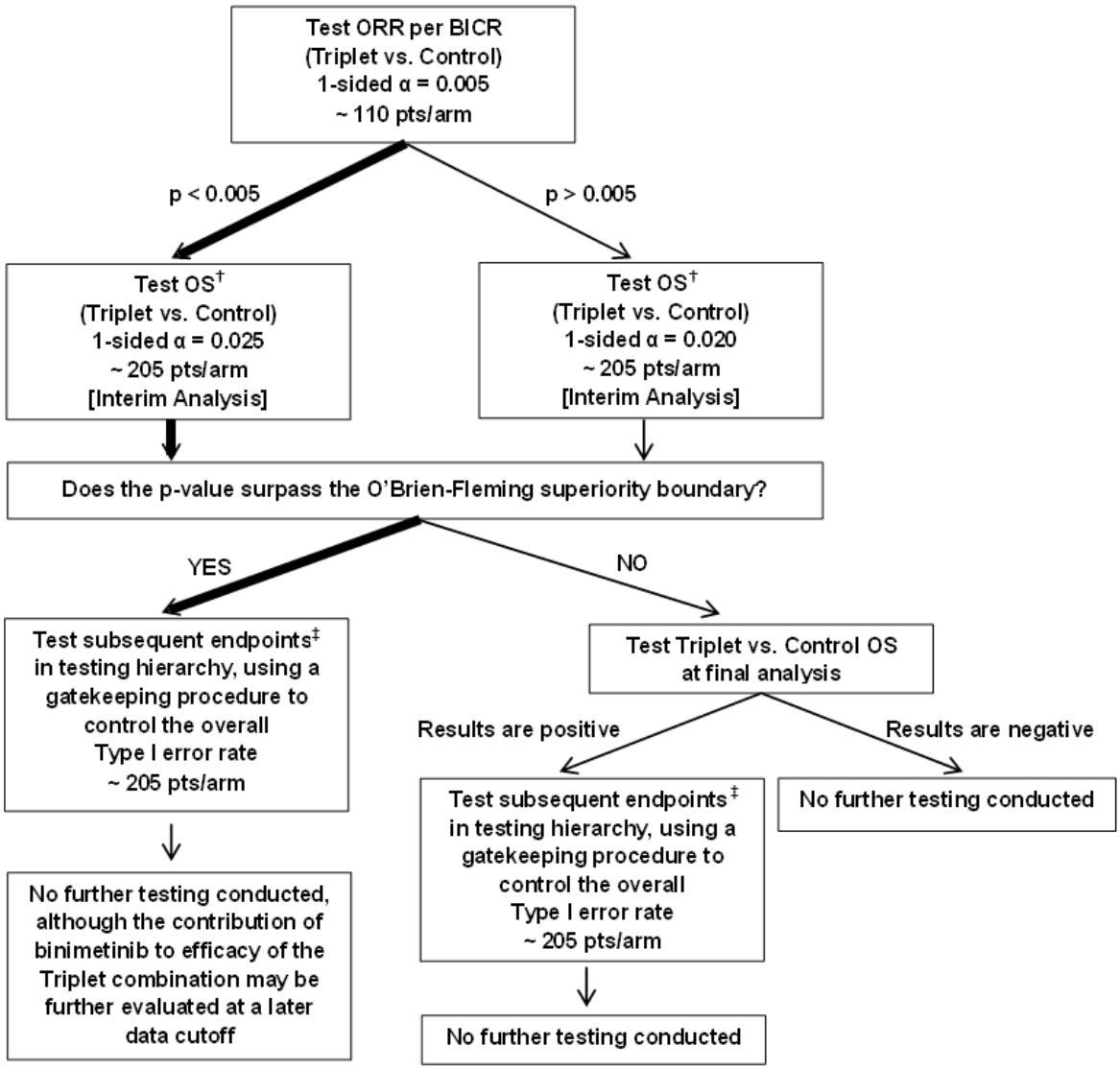
B.2.5.2 Hierarchical statistical testing

The type I error rate for the primary endpoints was controlled with the use of a fallback procedure described by Wiens and Dmitrienko (52). If the p value of the Enco+Bini with cetuximab vs control comparison of ORR at the primary analysis was <0.005, then the Enco+Bini with cetuximab vs control OS comparison was to be assigned a total one-sided alpha of 0.025 (Figure 2). Otherwise, it would remain at the assigned one-sided 0.020 level.

To incorporate testing of selected secondary endpoints, a gatekeeping procedure with hierarchical testing was used to account for the multiple comparisons (Figure 2). Specifically, if Enco+Bini with cetuximab vs control OS analysis was positive, the following endpoints were to be tested sequentially until a result that was not statistically significant was found. The endpoints would be tested in the following order:

1. OS of Enco with cetuximab vs control (key secondary endpoint).
2. ORR (per BICR) of Enco with cetuximab vs control.
3. PFS (per BICR) of Enco+Bini with cetuximab vs control.
4. PFS (per BICR) of Enco with cetuximab vs control.

Figure 2: Testing strategy for Phase 3 primary and secondary endpoints



Abbreviations: BICR, blinded independent central review; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pts, patients.
† A Lan-DeMets spending function that approximates O'Brien-Fleming boundaries will be used to account for the multiple (i.e. interim and final) analyses of OS; ‡ Subsequent endpoints would be tested in the following order: Enco with cetuximab vs control OS, Enco with cetuximab vs control ORR per BICR, Enco+Bini with cetuximab vs control PFS per BICR, and then Enco with cetuximab vs control PFS per BICR.
Bold arrows show the testing sequence actually performed based on initial analysis.

Planned interim analysis: An interim analysis was prospectively defined, which was planned for when three criteria were met:

- Approximately 9 months after randomisation of the 330th patient (i.e., to provide sufficient follow-up for responders).
- At least 188 OS events in the Enco+Bini with cetuximab and control arms combined.
- At least 169 OS events in the Enco with cetuximab and control arms combined.

ORR analysis by BICR for Enco+Bini with cetuximab arm vs control: The primary analysis of this outcome was to occur when the criteria for the initial analysis were met.

OS analysis for Enco+Bini with cetuximab arm vs control: An interim analysis for superiority or (non-binding) futility of the OS endpoint was also performed at the time of the interim analysis based on all available data.

At this initial analysis, the p-value of the primary ORR analysis of Enco+Bini with cetuximab vs control comparison was <0.005; as such the Enco+Bini with cetuximab versus control OS comparison was assigned a total one-sided α of 0.025 (See bold arrows in Figure 2 and Table 5). Subsequently, as the interim analysis for OS (Enco+Bini with cetuximab vs control) was found to exceed the superiority boundary, sequential testing of secondary endpoints was conducted at this point, as described above (See bold arrow in Figure 2).

Table 5: Hierarchical testing summary for efficacy endpoints

Primary/ Secondary	Endpoint		Criterion for significance (p value)	Actual p value
	Assessment	Treatment Arms		
Primary	ORR by BICR	Enco+Bini with cetuximab vs. control	0.005	<0.0001
	OS	Enco+Bini with cetuximab vs. control	0.0102	<0.0001
Key secondary	OS	Enco with cetuximab vs. control	0.0042	0.0002
Secondary	ORR by BICR	Enco with cetuximab vs. control	0.025	<0.0001
	PFS by BICR	Enco+Bini with cetuximab vs. control	0.0112	<0.0001
	PFS by BICR	Enco with cetuximab vs. control	0.0117	<0.0001

Abbreviations: BICR, blinded independent central review; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Continued OS follow-up (as well as other endpoints including ORR and PFS) was prospectively planned for a more mature comparison (15th August data cut-off).

B.2.5.3 Statistical hypothesis and methods of analyses

B.2.5.3.1.1 OS

OS (primary endpoint)

The following statistical null hypothesis for OS was to be tested:

$$H_0: S_{OS,A}(t) \leq S_{OS,C}(t)$$

where $S_{OS,A}(t)$ is the OS survival distribution function for the Enco+Bini with cetuximab arm and $S_{OS,C}(t)$ is the OS survival distribution function for the control arm.

The null hypothesis was tested using a stratified log-rank test against the α assigned to the endpoint based on the fallback procedure (described in Section B.2.5.3).

OS was described using the Kaplan-Meier (K-M) method, and the HR and 95% CIs were estimated using Cox proportional hazard models, stratified by randomisation stratification factors.

Futility and superiority boundaries for both the OS interim and final analyses were determined using a Lan DeMets (53) spending function that approximated O'Brien-Fleming stopping boundaries.

OS (secondary endpoint)

Secondary OS endpoints use the same approach as for the primary OS analysis.

B.2.5.3.1.2 ORR

ORR by BICR (primary endpoint)

The ORR by BICR for Enco+Bini with cetuximab versus control was tested based on the Phase 3 Response Efficacy Set and using the Cochran-Mantel-Haenszel test at a one-sided α of 0.005. Analysis of the confirmed responses was used for formal testing. The stratification factors used in the test were those used for randomisation and were based on IWRS randomisation information. For the primary analysis, ORR was presented by arm, along with 95% and 99% CIs. A similar analysis for ORR was performed on the FAS.

Secondary ORR endpoints

The secondary ORR endpoints were analysed in a similar manner to the primary ORR analyses for the Phase 3 Response Efficacy Set and the FAS. The Enco with cetuximab vs control comparison of ORR was formally tested using the Phase 3 Response Efficacy Set because the preceding endpoints in the testing hierarchy (Enco+Bini with cetuximab vs

control ORR, Enco+Bini with cetuximab arm vs control arm OS and Enco with cetuximab arm vs control arm OS) were observed to be statistically significant. As all patients in this analysis set were assumed to have sufficient follow-up for response, the full α assigned to the OS endpoints (i.e. one-sided 0.025) was applied to the Enco with cetuximab arm vs control arm ORR comparison.

ORR by local investigator was also assessed although this was not part of the hierarchical testing.

B.2.5.3.1.3 PFS

Progression-free survival was calculated for all patients in the FAS and analysed using the same approach as for OS. Comparisons of Enco with cetuximab vs control PFS and Enco+Bini with cetuximab vs control PFS were formally tested using the FAS because all of the preceding endpoints in the testing hierarchy were observed to be statistically significant (see Figure 2). A Lan-DeMets spending function that approximated O'Brien-Fleming stopping boundaries was applied in formal testing.

PFS by BICR was prioritised in the hierarchical testing. PFS by local investigator was also analysed although this was not part of the hierarchical testing.

B.2.5.3.1.4 Other outcomes

Analyses of DOR and TTR were performed using BICR and local investigator assessments and summarised using the K-M method for the FAS and Phase 3 Efficacy Response Set. No formal statistical test was performed for TTR.

EORTC QLQ-C30, FACT-C, EQ-5D-5L and PGIC were all assessed in the FAS and summarised with descriptive statistics. Time to definitive deterioration in HRQOL scores were presented as K-M curves.

B.2.5.4 Sample size and power calculation

Sample size (approximately 615) was driven by the secondary endpoint of OS in the Enco with cetuximab vs control comparison. For this comparison, it was calculated that 338 deaths would be required to give the trial 90% power to detect a HR for death of 0.70, with the use of a stratified log-rank test at a one-sided significance level of 0.025. This corresponds to a median OS of 7.1 months in the Enco with cetuximab arm and 5 months in the control arm.

The final OS analysis was planned to occur when at least 268 and 338 OS events had occurred in the combined Enco+Bini with cetuximab and control arms, and the combined Enco with cetuximab and control arms, respectively. With 268 events in the Enco+Bini with cetuximab and control arms, there would be approximately 90% power to detect a HR=0.67 at a one-sided significance level of 0.025.

The number of patients who would need to be included in the primary analysis of ORR in the Enco+Bini with cetuximab vs control comparison was based on an assumption that the ORR would be 10% in the control group and 30% in the Enco+Bini with cetuximab group; it was calculated that 110 patients per group would provide 88% power, at a one-sided significance level of 0.005, to show the higher ORR in the Enco+Bini with cetuximab group.

B.2.5.5 Sensitivity analyses and other supportive analyses

Several sensitivity analyses were to be conducted to support the primary analysis of OS and ORR, providing nominal p-values for descriptive purposes, as described below. Additional sensitivity analyses for key secondary endpoints including PFS were also conducted.

OS

- Using Per-Protocol Set.
- Unstratified Cox regression (FAS).
- Using multivariate stratified Cox regression to assess effect of potential prognostic factors; see Section B.2.5.5.2 for covariates.

ORR

- Using unstratified Chi-squared test.
- Using the FAS.
- Patients who had measurable disease at baseline (Phase 3 Response Efficacy Set).
- Using multivariate stratified Cox regression to assess effect of potential prognostic factors (Phase 3 Response Efficacy Set); see Section B.2.5.5.2 for covariates.

B.2.5.5.2 Multivariate stratified Cox regression

Multivariate stratified Cox regression included the following covariates:

- Randomisation stratification factors: ECOG PS status, prior irinotecan use, cetuximab source.

- Additional baseline factors: gender (male vs female); age (<65 vs ≥65 years); removal status of primary tumour (no resection/partial resection, complete resection); C-reactive protein (CRP) baseline level (≤ upper limit of normal [ULN] vs >ULN); side of tumour (left/right vs left vs right); number of organs involved based on target and non-target lesion assessment (≤2 vs 3+); presence of liver metastases at baseline, based on target and non-target lesion assessment (yes vs no); number of prior regimens (1 vs 2); prior oxaliplatin use (yes vs no). To avoid model instabilities, these covariates were only included if there were ≥10 patients in each category; microsatellite instability (MSI) status (high vs stable) was excluded from the model for this reason.

B.2.5.6 Data management and withdrawals

Missing data were imputed using rules specified in the SAP.

OS

If a death was not observed by the date of analysis cut-off, OS was to be censored at the date of last contact.

PFS

If death or disease progression was not observed, PFS was censored at the date of last adequate tumour assessment (i.e. at the date of last tumour assessment of CR, PR, StD) prior to cut-off date or date a subsequent anticancer therapy is started. If a PFS event was observed after more than one missing or inadequate tumour assessment, PFS was censored at the last adequate tumour assessment. If a PFS event was observed after a single missing or non-adequate tumour assessment, the actual date of event was used.

When a patient discontinued treatment for “disease progression” based on clinical deterioration, without documented evidence of progression based on RECIST v1.1, it was not to be considered as a PFS event.

Censoring rules applied to the PFS endpoint are described in Table 6.

Table 6: Censoring rules for PFS

	Situation	Event date	Outcome
A†	No baseline assessment	Date of randomisation	Censored
B	Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate tumour assessment‡	Censored
D	No progression	Date of last adequate tumour assessment‡	Censored
E	Treatment discontinuation due to "Disease progression" without documented progression, i.e., clinical progression based on investigator claim	N/A (not considered as an event, patient without documented PD should be followed for progression after discontinuation of treatment)	Information ignored
F	New antineoplastic therapy given	Date of last adequate tumour assessment‡	Censored

Abbreviations: PD, progressive disease, N/A, not applicable
† Patients with a first tumour assessment post-randomisation but prior to treatment start were considered as "No baseline assessment". If the patient died no later than the time of the second scheduled assessment as defined in the protocol, then a PFS event at the date of death was counted; ‡ tumour assessment with non-missing and non-unknown overall lesion response.

When no imaging/measurement was done at all at a particular time point, the patient was classed as "not evaluable" at that time point. If only a subset of lesion measurements were made at an assessment, usually the case was also considered "not evaluable" at that time point, unless convincing argument could be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

DOR

For DOR, responders who did not have a PD or death date by the data cut-off date were censored at their last adequate radiological assessment (i.e. at the date of last tumour assessment of CR, PR or StD) prior to the cut-off date or date when a subsequent anticancer therapy for mCRC was started.

TTR

For TTR, patients who did not have a CR or PR by the data cut-off date were censored for time to response at their last radiological assessment. Patients who received subsequent anticancer therapy prior to response were censored at their last radiological assessment prior to initiation of subsequent anticancer therapy.

B.2.5.7 Participant flow in the relevant randomised controlled trials

A total of 1,677 patients were screened for eligibility. In total, 665 patients were randomised in a 1:1:1 ratio to receive Enco with cetuximab (n=220), Enco+Bini with cetuximab (n=224) or investigator's choice of either irinotecan/cetuximab or FOLFIRI/cetuximab (Control; n=221). For further details, please refer to Appendix D, Section D.2.

B.2.6 Quality assessment: BEACON CRC

BEACON CRC is a large, global, multinational, multicentre, randomised, open-label, active-controlled, well conducted and methodologically robust Phase 3 study.

The study was approved by the institutional review board or independent ethics committee for each study centre and was conducted in accordance with the requirements of the regulatory authorities of each country and with the provisions of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council on Harmonisation.

All patients provided written informed consent. The steering committee and one of the sponsors (Array BioPharma) jointly designed the trial and reviewed the data. An independent Data Monitoring Committee was established to monitor data to ensure the continuing safety of the study patients.

BEACON CRC was conducted in an open-label manner; however, a number of steps were taken to minimise bias, as described in B.2.4.4.5. The randomisation schedule was created and managed by a third-party vendor and treatments were assigned according to a computerised central randomisation list using an IWRS.

A summary of quality assessment results is provided in Table 7.

Table 7: Quality assessment BEACON CRC

Trial number (acronym)	BEACON CRC
Was randomisation carried out appropriately?	Yes. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a computerised central randomisation list using an IWRS
Was the concealment of treatment allocation adequate?	Yes. See above
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Baseline characteristics were balanced between the groups.

Trial number (acronym)	BEACON CRC
Were the care providers, participants and outcome assessors blind to treatment allocation?	No. This was an open-label trial. To minimise bias, the Sponsor and their designee trial team, and the independent review committee were blinded to patient treatment assignment. The randomisation schedule was created and managed by a third-party vendor and treatments were assigned according to a central randomisation list using the IWRS.
Were there any unexpected imbalances in drop-outs between groups?	No. Discontinuation rates for any reason were similar across study arms. The majority of discontinuations across all arms were due to disease progression.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Analyses were conducted on the FAS, consisting of all randomised Phase 3 patients. Following the intention-to-treat principle, patients were analysed according to the treatment arm and stratum they were assigned to at randomisation.

Abbreviations: FAS, Full Analysis Set; IWRS, interactive web response system.

B.2.7 Clinical effectiveness results: BEACON CRC

BEACON CRC included three study arms:

- Enco with cetuximab
- Enco+Bini with cetuximab
- Control arm comprising investigator's choice of either:
  - Irinotecan with cetuximab, or
  - FOLFIRI with cetuximab

Key efficacy and safety results presented herein – that will inform decision making and are of direct relevance to future clinical practice in England – are those comparing the double regimen of Enco with cetuximab arm with the control arm. These include the key secondary (OS) and other secondary (ORR, PFS, DOR, TTR) endpoints for the study. PRO endpoints, including EQ-5D are also provided.

Results for the triple combination of Enco+Bini with cetuximab are not relevant to decision-making as marketing authorisation for the triple combination is not being sought at this time. Key efficacy results for this regimen, which include the primary endpoints of the study (OS and ORR for Enco+Bini with cetuximab versus control) and the secondary PFS endpoint are provided in Appendix A for completeness; other secondary efficacy endpoints and safety results for the Enco+Bini with cetuximab regimen are not provided.

Data are available from two data cut offs: the planned interim analysis, as of 11th February 2019 and the updated analysis, as of 15th August 2019. As the most mature dataset, the August 2019 results are presented as the key results, with the earlier February dataset presented in Appendix B.

For a full breakdown of the location of all results, see Table 8.

Table 8: BEACON CRC results presentation

Outcome	Enco with cetuximab vs control		Enco+Bini with cetuximab vs control	
	15th August 2019	11th February 2019	15th August 2019	11th February 2019
OS	Section B.2.7.1–B.2.7.6	Appendix L, Section L.2.1	Appendix L, Section L.2.2	Appendix L, Section L.2.2
ORR				
PFS				
DOR			Not presented	Not presented
TTR				
PROs				
Safety	Section B.2.11	Appendix L, Section L.3	Not presented	Not presented

Abbreviations: DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; TTR, time to response.

B.2.7.1 OS endpoints

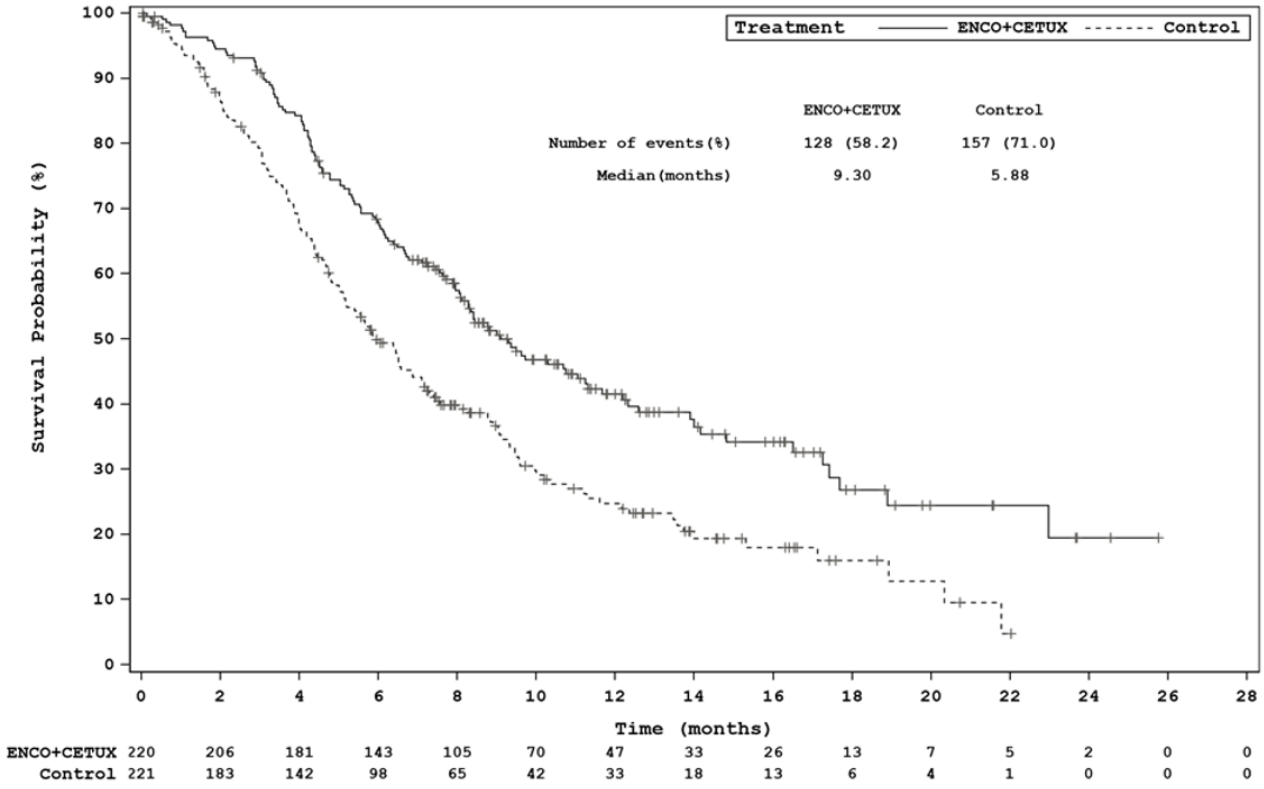
- As of the data cut-off date for the updated analysis (15th August 2019), the median duration of follow-up for survival was 12.8 months (Using a reverse K-M analysis).

B.2.7.1.1 OS Enco with cetuximab vs control, updated analyses, data cut-off 15th August 2019

- A total of 128 (58.2%) and 157 (71.0%) patients in the Enco with cetuximab and control arms, respectively, died on or before the data cut-off.
- Median OS was 9.30 months (95% CI: 8.05, 11.30) in the Enco with cetuximab group and 5.88 months (95% CI: 5.09, 7.10) in the control group, representing a clinically meaningful[h] improvement of 3.4 months (Figure 3 and Table 9).
- The risk of death was significantly lower (by 39%) in the Enco with cetuximab group than in the control group (HR: 0.61; 95% CI: 0.48, 0.77; one-sided p<0.0001).
- Estimated 6-month survival was [redacted]% in the Enco with cetuximab group and [redacted]% in the control group.
- The OS curves separate early (by 2 months after randomisation) and remain evenly separated over time (Figure 3).

[h] In CRC, ASCO recommend an increase in OS between 3–5 months and a HR of 0.67 translate into a clinically meaningful benefit (54).

Figure 3: OS for Enco with cetuximab vs control – FAS, data cut-off 15th August 2019



Abbreviations: CI, confidence interval; FAS, full analysis set.
Source: Kopetz Gastrointestinal Cancers Symposium 2020 (49), CSR Addendum Figure 5 (44).

Table 9: OS for Enco with cetuximab vs control – FAS, data cut-off 15th August 2019

	Enco with cetuximab (n=220)	Control (n=221)
Patients with events/Patients included in analysis (%)	128/220 (58.2)	157/221 (71.0)
Percentiles (95% CI), months		
Median (50th)	9.30 (8.05, 11.30)	5.88 (5.09, 7.10)
Stratified HR (95% CI)†,‡	0.61 (0.48, 0.77)	
Stratified log-rank (one-sided) p value†,‡	<0.0001	
Survival probability estimates, % (95% CI)§		
2 months	[redacted]	[redacted]
4 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
8 months	[redacted]	[redacted]
10 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
14 months	[redacted]	[redacted]
16 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; K-M, Kaplan-Meier; NR, not reached; OS, overall survival.
† Reference group for comparisons is control.
‡ Stratified by ECOG PS, source of cetuximab, and prior irinotecan use at randomisation.
§ Probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free probability estimates were obtained from K-M survival estimates. Greenwood formula was used for CIs of K-M estimates.
Source: CSR Addendum Table 9 and Table 14.2-2.1.1 (44).

B.2.7.1.1.1 Censoring and potential follow-up of OS

- 41.8% and 29.0% of patients in the Enco with cetuximab and control arms, respectively, were censored for the OS analysis; [redacted]% and [redacted]% of patients, respectively, were alive and ongoing in OS follow-up. Fewer patients in the Enco with cetuximab arm than in the control arm were censored because they withdrew consent ([redacted] censored patients and [redacted] censored patients, respectively). The majority of censored patients were last contacted ≤3 months prior to the data cut-off date.

B.2.7.1.1.2 OS supportive analyses

- A supportive multivariate Cox regression model stratified by study strata (ECOG PS, prior irinotecan use and cetuximab source) and adjusted for pre-specified baseline covariates was used to explore the consistency of treatment effect on OS.

- The analysis demonstrated that, after adjusting for the pre-specified baseline covariates, the OS comparison of Enco with cetuximab arm versus control was consistent with the primary OS analysis (HR [redacted]).
- Four pre-specified covariates also reached statistical significance: [redacted]).

B.2.7.2 ORR endpoints

B.2.7.2.1 ORR Enco with cetuximab vs control, updated analyses, data cut-off 15th August 2019

- The primary endpoint analysis for ORR was conducted on the Phase 3 Response Efficacy Set (the first 331 patients who underwent randomisation) for the February data cut only (see Appendix L, Section L.2.1.2). Analyses at the August data cut-off are based on the FAS and are presented in Table 10.
- ORR was significantly higher in the Enco with cetuximab group than in the control group; independently reviewed (BICR) confirmed ORR, assessed in the FAS, was 19.5% (95% CI: 14.5, 25.4) in the Enco with cetuximab group and 1.8% (95% CI: 0.5, 4.6) in the control group (one-sided p<0.0001).
- Response rates as assessed by local investigators were similar to those assessed by BICR.

Table 10: Confirmed tumour responses by BICR† – FAS, updated analyses, data cut-off 15th August 2019

Variable	Enco with cetuximab (N=220)	Control (N=221)
ORR: CR + PR, n (%)‡	43 (19.5)	4 (1.8)
95% CI	14.5, 25.4	0.5, 4.6
One-sided p vs. control	<0.0001	
BOR, n (%)‡		
CR	7 (3.2)	0 (0.0)
PR	36 (16.4)	4 (1.8)
St	117 (53.2)	59 (26.7)
PD	21 (9.5)	[redacted]

Variable	Enco with cetuximab (N=220)	Control (N=221)
Non-CR/Non-PD	[redacted]	[redacted]
Could not be evaluated according to RECIST§	32 (14.5)	70 (31.7)
DCR: CR+PR+StD+Non-PD/Non-CR, n (%)	167 (75.9)	69 (31.2)
95% CI	69.7, 81.4	25.2, 37.8
DOR months, median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Patients with DOR ≥6 months, n/total n of patients with a response (%)	[redacted]	[redacted]
Patients with ongoing response and <6 months follow-up, n/total n of patients with a response (%)	[redacted]	[redacted]
TTR (for patients with confirmed response) months, median	[redacted]	[redacted]
95% CI	[redacted]	[redacted]

Abbreviations: AE, adverse event; BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reported; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; StD, stable disease; TTR, time to response.
† All responses were confirmed and were assessed by BICR according to RECIST version 1.1. Percentages may not total 100 because of rounding; ‡ CR and PR were confirmed by repeat assessments performed ≥4 weeks after criteria for response were met.
Source: CSR Addendum Table 11; CSR Addendum Table 14.2-4.2.1; CSR Addendum Table 14.2-5.2.1 (44).

B.2.7.2.1.1 ORR sensitivity and supportive analyses

- Sensitivity analysis – unstratified analysis in the FAS – generated the same ORR and p value as the stratified analysis.
- A supportive multivariate Cox regression model stratified by study strata (ECOG PS, prior irinotecan use and cetuximab source) was used to explore the consistency of treatment effect on ORR when adjusting for pre-specified baseline covariates.
  - The analysis demonstrated that, after adjusting for pre-specified baseline covariates, the odds of a response in the Enco with cetuximab arm versus control was ~15-fold higher ([redacted]). This was consistent with a stratified univariate analysis, looking only at treatment group ([redacted]).

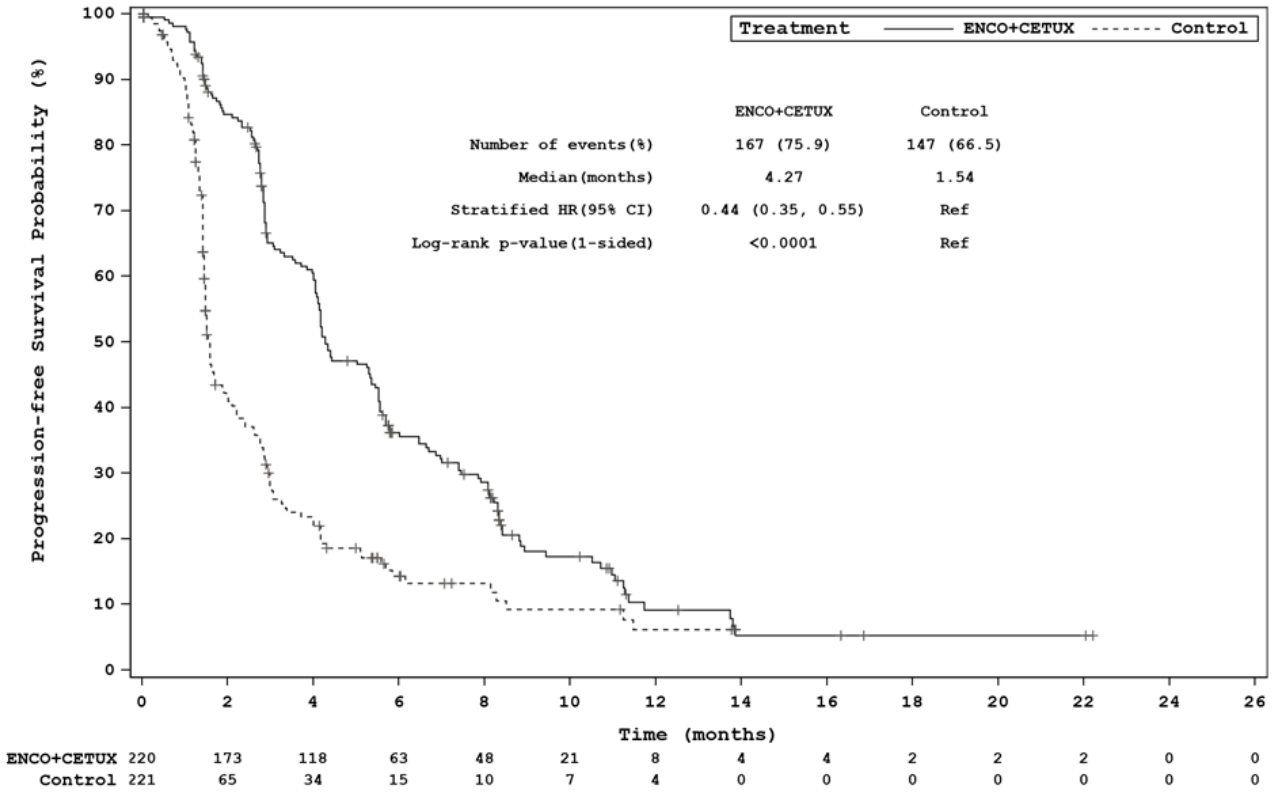
B.2.7.3 PFS endpoints

- As of the data cut-off date for the updated analysis (15th August 2019), the median follow-up for PFS was [redacted] months.

B.2.7.3.1 PFS Enco with cetuximab vs control, updated analyses, data cut-off 15th August 2019

- PFS by BICR was significantly longer in the Enco with cetuximab group versus the control (Figure 4).
- Median PFS was 4.27 months (95% CI: 4.07, 5.45) in the Enco with cetuximab group and 1.54 months (95% CI: 1.48, 1.91) in the control.
- The HR for disease progression or death was 0.44 (95% CI: 0.35, 0.55) in the Enco with cetuximab group as compared with the control (one-sided p<0.0001).
- PFS by local investigator was comparable to the PFS by BICR (HR: [redacted]; 95% CI: [redacted]), one-sided p<[redacted]).

Figure 4: PFS for Enco with cetuximab vs control – FAS, updated analyses, data cut-off 15th August 2019



Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival.
Source: CSR Addendum Figure 8 (44).

B.2.7.3.2 Additional PFS analyses, updated analyses, data cut-off 15th August 2019

- Supportive multivariate Cox regression analysis stratified by study strata (ECOG PS, prior irinotecan use and cetuximab source) and adjusted for pre-specified baseline covariates, confirmed the primary PFS analysis:
  - Enco with cetuximab arm versus control: HR for disease progression or death [redacted].

B.2.7.4 DOR endpoints

B.2.7.4.1 DOR Enco with cetuximab vs control, updated analyses, data cut-off 15th August 2019

- The K-M estimate of median DOR by BICR (FAS), calculated for confirmed responses, was [redacted] months (95% CI: [redacted]) in the Enco with cetuximab arm and [redacted] months (95% CI: [redacted]) in the control arm (Table 10); [redacted] patients in the control arm had confirmed responses of CR or PR.
- Results per local investigator (FAS) were similar to those assessed by BICR.

B.2.7.5 TTR endpoints

B.2.7.5.1 TTR Enco with cetuximab vs control, updated analyses, data cut-off 15th August 2019

- The K-M estimate of median TTR by BICR (FAS), calculated for confirmed responses, was [redacted] months (95% CI: [redacted]) in the Enco with cetuximab arm and [redacted] months (95% CI: [redacted]) in the control arm (Table 10), corresponding to the time of first assessment following treatment initiation.
- Results per local investigator (FAS) were similar to the BICR analysis.

B.2.7.6 Patient-reported outcomes

B.2.7.6.1 EORTC QLQ-C30

B.2.7.6.1.1 EORTC QLQ-C30 Enco with cetuximab vs control, updated analyses, data cut-off 15th August 2019

- Median EORTC QLQ-C30 global health status, and physical, emotional and social functioning scores were [redacted] in the Enco with cetuximab and control arms at baseline.

- The estimated median time to definitive 10% deterioration in the EORTC QLQ-C30 global health status score was longer in the Enco with cetuximab arm ([redacted] months) compared with the control arm ([redacted] months) (HR: [redacted]). Similar results were observed for the remaining EORTC scores.

B.2.7.6.2 FACT-C

B.2.7.6.2.1 FACT-C Enco with cetuximab vs control, initial analyses, data cut-off 15th August 2019

- Median FACT-C functional well-being, physical well-being, social/family well-being, emotional well-being, and colorectal cancer subscale scores were [redacted] in the Enco with cetuximab and control arms at baseline.
- The estimated median time to definitive 10% deterioration in the FACT-C functional well-being score was longer in the Enco with cetuximab arm ([redacted] months) versus control ([redacted] months) (HR: [redacted]). Similar results were observed for the remaining FACT-C subscales.

B.2.7.6.3 EQ-5D-5L

B.2.7.6.3.1 EQ-5D-5L Enco with cetuximab vs control, initial analyses, data cut-off 15th August 2019

- Median EQ-5D-5L VAS and utility index scores were [redacted] in the Enco with cetuximab and control arms at baseline.
- The estimated median time to definitive 10% deterioration in the EQ-5D-5L (VAS and utility index scores) was [redacted] in the Enco with cetuximab arm [redacted] months) compared with the control arm ([redacted] months), with stratified HRs of [redacted] and [redacted], respectively.

B.2.7.6.4 PGIC

B.2.7.6.4.1 PGIC Enco with cetuximab vs control, initial analyses, data cut-off 15th August 2019

The proportion of patients who responded to the PGIC questionnaire with “much improved” or “very much improved” at Cycles 2, 3 and 4 was [redacted] in the Enco with cetuximab arm than the control (Cycle 2: [redacted] Enco with cetuximab, [redacted] control; Cycle 3: [redacted] Enco with cetuximab, [redacted] control; Cycle 4: [redacted] Enco with cetuximab, [redacted] control). This proportion remained in favour of Enco with cetuximab through later cycles; measurements from cycle 11 onwards became uncertain with <10 patients available in the control arm.

B.2.7.7 BEACON CRC efficacy conclusion

- BEACON CRC is the first and only Phase 3 RCT designed specifically for patients with BRAF V600E-mutant mCRC, whose disease had progressed after one or two prior regimens in the metastatic setting.
- The use of targeted therapy with encorafenib, in combination with cetuximab significantly improved OS, PFS and ORR, while sustaining patient's HRQoL across a number of disease-specific and generic tools compared with standard of care therapy.
- The significant OS improvements observed with this new targeted therapy meet NICE end-of-life criteria and represent a substantial step forward in the treatment options available for this patient group, whose prognosis can be extremely poor.

B.2.8 Subgroup analysis: BEACON CRC

Pre-planned subgroup analyses of OS, ORR and PFS were performed for each baseline stratification factor and other relevant baseline variables for which at least 10 patients were available in the considered subgroup. Subgroups were prespecified as listed in the SAP. Subgroup analyses were performed based on ECOG PS, prior use of irinotecan, cetuximab source, region, number of prior regimens, race, age, gender, number of organs involved at baseline, MSI, BRAF V600E mutation per central assessment, baseline CEA, baseline CRP, removal status of primary tumour, side of tumour, presence of liver metastases at baseline. The OS and PFS analyses were to include K-M summaries and HRs (95% CI) from unstratified Cox models. Forest plot representations were also provided.

Demographics and disease characteristics for subgroups were not defined.

Results were generally consistent with overall results (15th August data cut-offs), with HRs (OS, PFS) and ORs generally in favour of Enco with cetuximab versus control. It should be noted that for many of the analyses, the number of patients included in each subgroup was small which may affect interpretation of the data.

Full results for the 15th August data cut-offs are provided in Appendix E.

B.2.9 Meta-analysis

BEACON CRC is the only RCT reporting on the efficacy and safety of Enco with cetuximab in patients with BRAF V600E-mutant mCRC. Therefore, a meta-analysis was not required.

B.2.10 Indirect and mixed treatment comparisons

Indirect treatment comparison (ITC) summary

- The feasibility of conducting an network meta-analysis (NMA) was explored to determine if relative estimates of effectiveness between the Enco with cetuximab regimen and FOLFIRI or trifluridine-tipiracil regimens could be derived in the BRAF-mutant mCRC population.
- Since BEACON CRC is the only Phase 3 RCT specifically investigating the BRAF V600E-mutant mCRC population there is a general paucity of data from RCTs and observational studies to allow indirect comparison with relevant comparator treatments specifically in BRAF-mutant mCRC populations.
- Using the single RCT study (20050181/NCT0039183) which did report limited BRAF-mutant subgroup data (Total N=45) and that could be linked to BEACON CRC via a common comparator, an ITC was feasible for Enco with cetuximab versus FOLFIRI.
- The ITC was only possible by applying two assumptions of clinical equivalence which were supported by the literature and expert opinion:
  - 1. Equivalence between the EGFR inhibitors cetuximab and panitumumab; and
  - 2. Equivalence between FOLFIRI and irinotecan
- These assumptions allowed a connected network to be formed to conduct an **ITC of Enco with cetuximab compared with FOLFIRI**, by assuming equivalence of FOLFIRI plus cetuximab or irinotecan plus cetuximab (BEACON CRC control arm) and FOLFIRI plus panitumumab (20050181/NCT0039183).
- The results suggest that Enco with cetuximab is associated with a statistically significantly lower hazard of death (OS HR 0.39 [95% CI: 0.19, 0.81]) and progression (PFS HR 0.30 [95% CI: 0.14, 0.68]) compared with FOLFIRI.
- The main strength of the ITC was that it allowed evidence for FOLFIRI, when administered alone, to be indirectly compared with the encorafenib regimen and

thus generate an estimate of effectiveness for this comparator, as per the NICE scope. It should also be acknowledged that the ITC is subject to the following limitations:

  - having to assume that EGFR inhibitors are equivalent (cetuximab = panitumumab) to allow the network to be formed;
  - outcome estimates for FOLFIRI are only available from small post-hoc subgroup analyses (N=45) and were not powered to detect treatment differences;
  - baseline characteristics are only available for the overall trial population for the FOLFIRI study and hence conclusions of comparability specifically between BRAF-mutant populations cannot be made with certainty.

- An ITC was not possible versus trifluridine-tipiracil due to a complete absence of data in the BRAF-mutant mCRC population. A naïve comparison is possible using data for a population of patients for whom BRAF status was not defined but would have comprised of predominantly BRAF wild-type patients (RECOURSE study, Mayer 2015). Using this data would have led to a significant overestimation in treatment effect if not adjusted. Therefore, for cost-effectiveness analysis this data is adjusted for the poorer prognosis observed in patients with BRAF-mutation compared with BRAF wild-type; this approach is subject to greater uncertainty than the ITC.

B.2.10.2 Methodology

B.2.10.2.1 Background

The BEACON CRC trial investigated the intervention for this appraisal (namely Enco with cetuximab) in comparison with a control arm comprising investigator's choice of FOLFIRI or irinotecan in combination with cetuximab. As described in Table 1, the comparators of relevance to the anticipated place in therapy for Enco with cetuximab and included in the company decision problem are FOLFIRI and trifluridine-tipiracil.

To enable comparisons of Enco with cetuximab and FOLFIRI, two options were available:

- Use the BEACON CRC control arm as a proxy for FOLFIRI relative effectiveness, by assuming that FOLFIRI with cetuximab and irinotecan with cetuximab have an

equivalent effect (see Section B.2.10.2.4 for further discussion). This method would be considered as a conservative approach to estimating relative effectiveness of Enco with cetuximab versus FOLFIRI, as it would be assumed that cetuximab would contribute some benefit to the BEACON CRC control arm.

- An alternative method was to explore the feasibility of conducting an NMA using studies that investigated FOLFIRI when administered alone.

To enable comparisons of Enco with cetuximab and trifluridine-tipiracil relative effectiveness estimates for Enco with cetuximab versus trifluridine-tipiracil are not available directly from the BEACON CRC trial and hence an indirect source had to be considered.

In this context systematic reviews of the RCT and non-RCT literature were conducted to enable an NMA feasibility assessment to derive indirect estimates of relative treatment effectiveness.

B.2.10.2.2 Study selection

The RCT systematic review described in Appendix D, Section D.1.1 identified a total of 11 unique RCTs for populations of relevance to the anticipated positioning of Enco with cetuximab – namely second-line or later lines of therapy in patients with BRAF V600E-mutant mCRC (28, 42, 43, 45, 55-61). These studies were considered for potential inclusion in network meta-analysis.

In terms of patient population, of the 11 RCTs identified in the review:

- Three RCTs were conducted in exclusively BRAF V600E-mutant mCRC populations (45, 55, 61).
- The remaining eight RCTs identified were conducted in mixed populations but reported subgroup results for BRAF V600E-mutant mCRC subpopulations (28, 42, 43, 56-60).

In terms of the intervention and comparators of relevance to the NICE scope the following data was identified:

- **Enco with cetuximab:** Two RCTs report trial arms investigating Enco with cetuximab.
  - BEACON CRC (55), which is the pivotal Phase 3 study for Enco with cetuximab and has been and described in detail in Section B.2.4 onwards. For the purposes

of network meta-analysis feasibility and subsequent ITC analyses conducted, the most mature dataset from August 2019 was utilised. This information was taken from the CSR addendum and associated files as described in Section B.2.4. The Kopetz 2019 abstract identified in the systematic review was therefore disregarded for subsequent analyses.

  - Tabernero 2016 (45) reported on a Phase 1b/2 study. Encorafenib was administered at a lower dose than recommended in the licence (200 mg QD vs 300 mg QD) and hence this study was disregarded from further analysis.

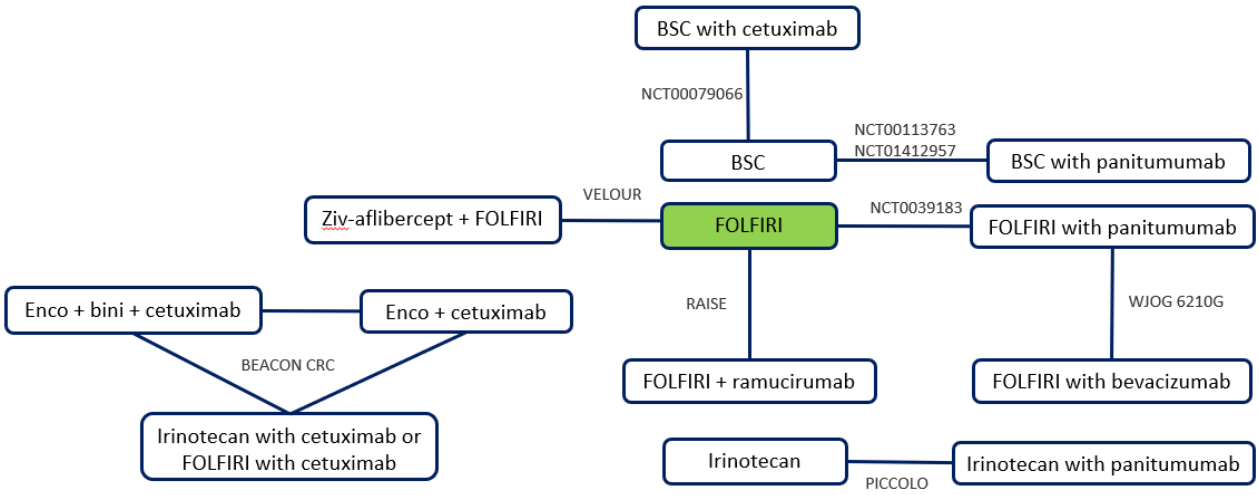
- **FOLFIRI:** Three RCTs report trial arms investigating FOLFIRI (28, 42, 43). A further study included FOLFIRI but only when given in combination with bevacizumab or panitumumab (60).
- **Irinotecan**: A single RCT reports a trial arm investigating irinotecan (58). Although included in the NICE scope, irinotecan is not considered to be a relevant comparator is therefore not being considered in the company decision problem (see Table 1).
- **Trifluridine-tipiracil**: No RCTs investigated trifluridine-tipiracil.
- **BSC:** three studies were identified which included BSC (56, 57, 59). Although included in the NICE scope, BSC is not considered to be a relevant comparator for the point in the patient pathway where Enco with cetuximab will be used and is therefore not considered in the company decision problem (see Table 1).

One study (SWOG 1406) investigated combination treatment of irinotecan and cetuximab with or without vemurafenib (61). This study was not considered further as it didn't include any of the interventions of relevance to the NICE scope.

B.2.10.2.3 Options considered for evidence synthesis

Following elimination of the SWOG 1406 and Tabernero 2016 studies (45, 61), the remaining RCTs were mapped based on the connectivity of randomised interventions between the BEACON CRC trial and the eight comparator RCTs conducted in mixed with BRAF V600E-mutant mCRC populations (28, 42, 43, 56-60); the evidence mapping is shown in Figure 5.

Figure 5: Mapping RCTs



Abbreviations: Bini, binimetinib; BSC, best supportive care; Enco, encorafenib; FOLFIRI, folinic acid/fluorouracil/irinotecan.
Green nodes represent comparators of interest in the company decision problem.
Sources: BEACON CRC, see section B.2.4; PICCOLO (58); RAISE (28); VELOUR (43); WJOG 6210G (60); 20050181/NCT0039183 (42); CO.17/NCT00079066 (59); 408/NCT00113763 (57); 20100007/NCT01412957 (56).

A connected evidence network inclusive of relevant comparators for the company decision problem was not feasible due to: i) a lack of common comparator treatment arms and ii) comparator treatment arms were not relevant to the NICE scope (Figure 5).

Although observational evidence is considered to be of lower quality and will be subject to higher levels of bias versus RCT evidence, in the absence of a connected evidence network based on RCT data alone, observational evidence was also considered for evidence synthesis. Based on a systematic review (see Appendix D, Section D.1.2), one Phase 1b study (Van Geel 2017 (62)), which assessed Enco with cetuximab versus Enco with cetuximab and alpelisib in BRAF-mutant mCRC patients was identified; this study was disregarded for evidence synthesis as it was a dose escalation study with a maximum encorafenib dose of 450 mg QD which exceeds the licensed dose of 300 mg QD and only reported PFS. None of the other trials investigated any comparators of interest. Incorporation of observational evidence into the evidence network was therefore discounted.

B.2.10.2.4 Analysis used: Grouped treatment nodes ITC

In the absence of a connected network the approach adopted was grouped treatment nodes ITC. Based on the available literature and expert opinion (see Table 1 footnote “a”) it was possible to apply assumptions of equivalence between specific treatments, which

then allowed these interventions to be grouped and enable ITC. The grouping assumptions were as follows:

- **Equivalence of FOLFIRI and irinotecan:** The BEACON CRC RCT included a control arm comprising investigator's choice of either FOLFIRI or irinotecan in combination with cetuximab. The choice of control therapies for this study was made partly in the context that these two therapies would provide approximately equivalent efficacy. In two head-to-head comparisons of second-line therapy with FOLFIRI and irinotecan in mCRC patients without specific molecular characterisation of their disease (i.e. BRAF status not established), the treatment groups did not differ statistically in OS or PFS (63, 64). The assumption that FOLFIRI and irinotecan would be equivalent in effectiveness was deemed to be clinically plausible based on expert opinion elicited for the current appraisal (see Table 1 footnote "a").
- **Equivalence of cetuximab and panitumumab:** Cetuximab and panitumumab exert their effects on CRC through inhibition of EGFR, and it seems plausible to assume a class effect. In the TA assessment of the two therapies, NICE concluded cetuximab and panitumumab were likely to have similar effectiveness in treating RAS wild-type mCRC (TA439) and the clinical experts consulted during that appraisal considered the two therapies to be equally effective (37). Expert opinion sought by Pierre Fabre for the current appraisal of Enco with cetuximab confirmed this assumption.

B.2.10.2.5 ITC networks

ITC of Enco with cetuximab compared with FOLFIRI

The assumption of grouping treatments enabled an ITC between Enco with cetuximab and FOLFIRI using study 20050181/NCT0039183 for FOLFIRI (42) and BEACON CRC for Enco with cetuximab. In this ITC, equivalence of FOLFIRI plus cetuximab or irinotecan plus cetuximab (BEACON CRC) and FOLFIRI plus panitumumab (20050181/NCT0039183) had to be assumed.

A network diagram overview of the ITC network for Enco with cetuximab versus FOLFIRI is presented in Figure 6. A table summarising the trials used to conduct the ITC is presented in Table 11. Although the FOLFIRI trial (20050181/NCT0039183) did report efficacy outcomes for the BRAF-mutant subpopulation, notably the study was not stratified by BRAF-mutation status and only reported baseline characteristics for the overall trial population and not for the BRAF-mutant subpopulation.

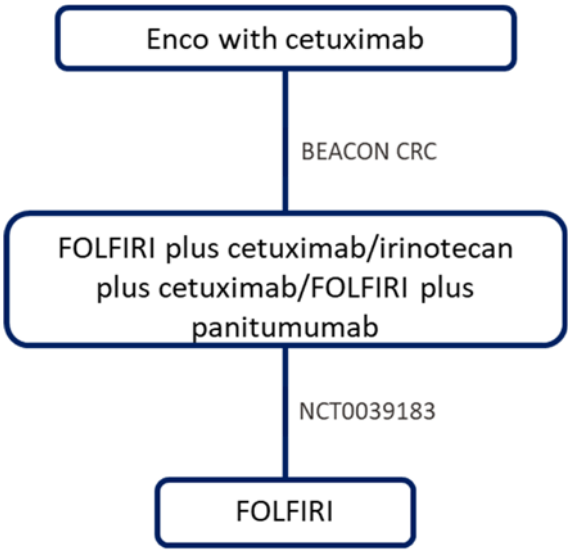
ITC of Enco with cetuximab compared with trifluridine-tipiracil

No RCTs including BRAF-mutant subgroups were identified to allow an ITC for trifluridine-tipiracil. The remaining option was to consider a naïve comparison of Enco with cetuximab versus trifluridine-tipiracil using data for the comparator from an mCRC population for which BRAF-mutant status was not reported; this approach is described in Section B.2.10.5.

Excluded trials

Reasons for exclusion of the remaining nine RCTs is provided in Appendix D, Table 11.

Figure 6: Network diagram for the ITC of Enco with cetuximab versus FOLFIRI



Abbreviations: Enco, encorafenib; FOLFIRI, folinic acid/fluorouracil/irinotecan; ITC, indirect treatment comparison.
Sources: BEACON CRC, see Section B.2.4; 20050181/NCT0039183 (42).

Table 11: Summary of the trials used to carry out the ITC

	Enco with cetuximab	Irinotecan plus cetuximab or FOLFIRI plus cetuximab	FOLFIRI
BEACON CRC	Yes	Yes	
20050181/NCT0039183 (42)		Yes	Yes

Abbreviations: Enco, encorafenib; FOLFIRI, folinic acid/fluorouracil/irinotecan; ITC, indirect treatment comparison.

B.2.10.2.6 Additional methodology

Further methodology, including tabulated summaries of the baseline characteristics and outcomes measured in the studies relevant to the ITC, methods of analysis and risk of bias assessment are provided in Appendix D, Section D.1.3.

B.2.10.3 Results

The results of the ITC are presented in Table 12 and suggest that Enco with cetuximab is associated with a statistically significantly lower hazard of death (OS) and progression (PFS) compared with FOLFIRI.

As there are only single trials for the pair-wise comparison contributing to the ITC it is not possible to conduct a statistical assessment of heterogeneity.

Table 12: Grouped nodes ITC results: Enco with cetuximab vs. FOLFIRI

Intervention	ITC HR (95% CI)		ITC HR (95% CI)	
	OS	PFS	PFS	PFS
Enco with cetuximab	0.39 (0.19, 0.81)	0.30 (0.14, 0.68)	comparator	comparator
FOLFIRI	comparator	comparator	2.56 (1.23, 5.26)	3.33 (1.47, 7.14)

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; vs., versus.
†Results presented in both directions for ease of interpretation (with FOLFIRI as comparator for comparison with BEACON CRC results, and with Enco with cetuximab as comparator for application in the cost-effectiveness model).

B.2.10.4 Uncertainties in the ITC

The main strength of the ITC was that it allowed evidence for FOLFIRI, when administered alone, to be indirectly compared with the encorafenib regimen and thus generate an estimate of effectiveness for this comparator, as per the NICE scope. It should be acknowledged however that the ITC is subject to the following limitations which may create some uncertainty in the estimates derived:

Assumed equivalence of EGFR inhibitors

- The EGFR inhibitors cetuximab and panitumumab had to be assumed equivalent to form common comparator treatment nodes and form connected networks. As described in B.2.10.2.4 this assumption is well-supported by conclusions drawn in NICE TA439 and clinical expert opinion.

Assumed equivalence of FOLFIRI with cetuximab and irinotecan with cetuximab

- FOLFIRI with cetuximab and irinotecan with cetuximab had to be assumed to be equivalent to allow the BEACON CRC control arm to be used to form connected networks for both the FOLFIRI ITC. As described in B.2.10.2.4 this assumption is broadly well-supported by the literature and expert opinion.

Outcomes data and sample size

- Whereas BEACON CRC was specifically designed and powered to determine treatment differences across the BRAF-mutant population enrolled, the BRAF-mutant subgroup analysis of outcomes collected during the original FOLFIRI study was exploratory (not defined in the original study protocol), the trial was not stratified for, and was not powered to detect, treatment differences in this specific patient group (42). The approximate 10-fold smaller BRAF-mutant population size in the FOLFIRI trial (N=45) relative to BEACON CRC (N=441) make the comparator outcome estimates more uncertain, potentially reflected in the wider 95% CIs observed around the OS/PFS HRs from the FOLFIRI trial.

Baseline characteristics

- Although the BRAF-mutant mCRC population in BEACON CRC represented the entire trial population (n=441 across relevant arms), in the FOLFIRI trial BRAF mutations were only present in a small subpopulation (10.7%; n=45/421). Although the baseline characteristics of BEACON CRC and the overall FOLFIRI trial were broadly consistent (Appendix D, Section D.1.3.2), baseline characteristics were not available for the BRAF-mutant subpopulation of the FOLFIRI trial. As such an assessment of comparability between BRAF-mutant populations across the two trials could not be made. Due to the limited number of studies in the ITC it was not possible to explore the uncertainties of this assumption.

The relative merits of using the results of the ITC or using evidence directly from BEACON CRC in deriving estimates of effectiveness for use in cost-effectiveness analyses are discussed further in Section B.2.14.2.2.4.

B.2.10.5 Trifluridine-tipiracil naïve comparison

The systematic reviews did not identify any studies that reported data for trifluridine-tipiracil in populations or subpopulations of patients with BRAF V600E-mutant mCRC that could be incorporated into an evidence network; for this reason an ITC was not feasible.

However, the RCT review did identify three RCTs that investigated trifluridine-tipiracil in mCRC populations for whom BRAF-mutation status had not been determined and reported K-M survival curves for OS and PFS (65-67). Two of the trials were conducted exclusively in Asian populations (Xu 2018 N=406 and Yoshino 2012 N=169 (65, 67)) and a single trial – Mayer 2015 – was conducted globally and comprised the largest patient

population (N=800; Japan, US, Europe and Australia) (66). For these reasons, Mayer 2015 was deemed most appropriate to consider in a naïve comparison with BEACON CRC to generate a relative treatment effect estimate for Enco with cetuximab compared with trifluridine-tipiracil.

Mayer 2015 (66) report a double-blind Phase 3 trial (RECOURSE) that investigated trifluridine-tipiracil (n=534) or placebo (n=266) in patients with mCRC whose cancer had been refractory to antitumour therapy or who had had clinically significant adverse events (AEs) that precluded the re-administration of those therapies. Median age was 63 years, 61% were male, and all had ECOG PS of 0 or 1. All patients had received at least two prior regimens, with the majority having had four or more (61%). KRAS proto-oncogene, GTPase (KRAS) mutations and KRAS wild-type was present in 51% and 49% of patients, respectively; BRAF status was not reported. Outcomes data for OS and PFS are summarised in Table 13.

Table 13: Summary of outcomes data from RECOURSE

Study	Treatment arm	Sample size	Population	Trial reported results, median in months (95% CI)†	
				OS	PFS
RECOURSE (66)	Trifluridine-tipiracil	534	KRAS wild-type/ KRAS mutant	7.1 (6.5, 7.8)	2.0 (1.9 to 2.1)
	Placebo	266		5.3 (4.6, 6.0)	1.7 (1.7

Abbreviations: CI, confidence interval; K-M, Kaplan-Meier; KRAS, KRAS proto-oncogene, GTPase; OS, overall survival; PFS, progression-free survival.
† Outcomes presented for information only. For cost-effectiveness analysis the K-M curves for OS and PFS for the trifluridine-tipiracil arm were digitised and recreated for use in the cost-effectiveness model.

It is recognised that outcomes in patients with BRAF-mutant mCRC can be substantially worse than in patients without these mutations (e.g. median OS 4.2 months in BRAF-mutant mCRC vs 15.5 months in RAS/BRAF wild-type for FOLFIRI at second-line (28)). Although the RECOURSE study did not provide information on the BRAF status of enrolled patients it did report that 51% had KRAS mutations. It is known that BRAF and KRAS mutations are mutually exclusive (25), while BRAF mutations occur in patients with KRAS wild-type at a ratio of approximately 1:10 (25). Accordingly, it may be estimated that ~5% of patients in the RECOURSE study may have had BRAF-mutations. This is consistent with UK studies which report incidence of BRAF-mutant CRC at around 8% of all CRC cases (23, 24). This suggests that using outcomes directly from the RECOURSE study to estimate the effectiveness of trifluridine-tipiracil in a BRAF-mutant population may significantly overestimate its effectiveness relative to Enco with cetuximab.

A potential option is to attempt to adjust the effectiveness outcomes from RECOURSE by the relative effect seen in BRAF-mutant and BRAF wild-type populations. Three studies identified in the RCT systematic review reported a HR for BRAF wild-type versus BRAF-mutant mCRC for at least one survival outcome (OS and/or PFS) (42, 56, 59). Peeters 2015 was the only study that reported a HR for both OS and PFS and also included the largest number of patients that had BRAF mutations (42); using this study provides relative estimates of effect (HR, [95% CI]) for BRAF wild-type versus BRAF-mutant for OS and PFS of 0.25 (0.18, 0.36) and 0.28 (0.20, 0.40), respectively. The reciprocals (1/HR) can be used to adjust the K-M curves for OS and PFS from Mayer to provide estimates of effectiveness that may be more appropriate for the BRAF-mutant population and can be implemented in the cost-effectiveness analysis.

Cost-effectiveness analyses using the K-M curves from Mayer 2015 which are then adjusted using the Peeters 2015 HRs are described in the cost-effectiveness Section B.3.

B.2.11 Adverse reactions

B.2.11.1 BEACON CRC (Data cut-off 15th August 2019)

AE data were recorded in the Phase 3 randomised portion of the BEACON CRC study. Data for the Safety Set (received at least one dose of study drug and had at least one post-treatment assessment), including 216 patients in the Enco with cetuximab arm and 193 patients in the control arm, is presented in this section. The control arm comprised investigator's choice of either FOLFIRI with cetuximab or irinotecan with cetuximab.

The safety analysis presented herein represents the latest data available from the 15th August 2019 data cut-off for the Enco with cetuximab and control arms of the study and will be submitted to the EMA as part of the marketing authorisation application for Enco with cetuximab. Safety data from the 11th February data cut is presented in Appendix L, Section L.1.3. Safety data for the Enco+Bini with cetuximab arm (n=222) is not presented.

B.2.11.1.1 Duration of exposure

- Median duration of exposure to study treatment (based on observed duration and not distinguishing between patients who discontinued or were ongoing) was [redacted] weeks in the Enco with cetuximab arm and [redacted] weeks in the control arm (Table 14).
- Within the Enco with cetuximab arm, median duration of exposure to each study drug component was similar (Enco, [redacted]; cetuximab, [redacted] weeks, respectively).
- K-M estimates of median exposure were [redacted] weeks in the Enco with cetuximab arm and [redacted] weeks in the control group (patients discontinuing by data cut-off date were considered events; patients still on treatment were censored).
- [redacted]% received ≥16 weeks of study treatment in the Enco with cetuximab arm; by comparison only one-fifth of patients in the control arm ([redacted]%) received ≥16 weeks of study treatment.
- Exposure versus planned dose (i.e. median relative dose intensity [RDI]) was high in the Enco with cetuximab arm (Enco, [redacted]%; cetuximab, [redacted]%), as compared with control (Cetuximab, [redacted]%; irinotecan, [redacted]%; 5-fluorouracil, [redacted]%; folinic acid, [redacted]%).

Table 14: Duration of exposure to study treatment – Safety set, data cut-off 15th August 2019

	Enco with cetuximab			Control				
	Enco N=216	Cetuximab N=216	Enco with cetuximab N=216	Cetuximab N=193	Irinotecan N=193	5-FU N=107	Folinic Acid N=107	Control N=193
Duration of exposure (weeks)								
N	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	[redacted]
Median	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	[redacted]
Exposure ≥16 weeks, n (%)	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR	[redacted]
RDI categories, n (%)								
<50%	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA
50 to <80%	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA
80 to <100%	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA
=100%	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA
>100%	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA
RDI (%)								
N	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA
Mean (SD)	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA
Median	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA
Min–Max	[redacted]	[redacted]	NA	[redacted]	[redacted]	[redacted]	[redacted]	NA

Abbreviations: 5-FU, 5-fluorouracil; Max, maximum; Min, minimum; NA, not applicable; NR, not reported; RDI, relative dose intensity; SD, standard deviation.
Relative Dose Intensity = 100*[Dose Intensity/Planned Dose Intensity]. Only control arm patients receiving FOLFIRI with cetuximab were eligible to receive 5-FU and folinic acid.
Source: CSR Addendum Table 3 and Table 4 (44).

B.2.11.1.2 Adverse events

An overview of AE data from BEACON CRC is provided by treatment arm for the safety set (Table 15).

Table 15: Summary of deaths and AEs – Safety set, data cut-off 15th August 2019

Category	Enco with cetuximab N=216		Control N=193	
	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)
On-treatment deaths†	[redacted]	[redacted]	[redacted]	[redacted]
On-treatment AEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
AE, treatment-related (suspected)	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]

Category	Enco with cetuximab N=216		Control N=193	
	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)
Serious AEs, treatment-related (suspected)	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring additional therapy	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring dose interruption of any study drug	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring dose reduction of any study drug	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation of any study drug	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation of all study treatment	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.
† [redacted].
Source: August update Table 14.3-1.1.1; August update Table 14.3.1-1.1.1; August update Table 14.3.1-1.40 (50).

Table 16 presents a summary of AEs, regardless of relationship to study drug, by preferred term, treatment and severity (all grades and maximum Grade 3+).

- The most frequently reported AEs (>30% of patients) by preferred term were mostly similar across the treatment arms:
  - **In the Enco with cetuximab arm:** diarrhoea [redacted], nausea [redacted], fatigue [redacted], decreased appetite [redacted] and dermatitis acneiform [redacted]);
  - **In the control arm:** diarrhoea [redacted], nausea [redacted], dermatitis acneiform [redacted] and vomiting [redacted]).
- The most frequently reported Grade 3+ AEs (>5.0% of patients) by preferred term:
  - **In the Enco with cetuximab arm:** were anaemia [redacted]);
  - **In the control arm:** were diarrhoea (10.4%), neutropenia [redacted], neutrophil count decreased [redacted], anaemia [redacted], and, abdominal pain (5.2%), asthenia (5.2%).

Table 16: AEs, regardless of relationship to study drug, by preferred term – overall (≥10% in any treatment arm) or Grade 3+ (≥2% in any treatment arm) – Safety set, data cut-off 15th August 2019

Preferred term	Enco with cetuximab N=216		Control N=193	
	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)
Any Adverse Event†	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea†	[redacted]	6 (2.8)	[redacted]	20 (10.4)
Nausea	[redacted]	1 (0.5)	[redacted]	3 (1.6)
Fatigue†	[redacted]	9 (4.2)	[redacted]	9 (4.7)

Preferred term	Enco with cetuximab N=216		Control N=193	
	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)
Decreased appetite†	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis acneiform†	[redacted]	1 (0.5)	[redacted]	5 (2.6)
Abdominal pain†	[redacted]	7 (3.2)	[redacted]	10 (5.2)
Vomiting†	[redacted]	3 (1.4)	[redacted]	6 (3.1)
Asthenia†	[redacted]	8 (3.7)	[redacted]	10 (5.2)
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia†	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Melanocytic naevus	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea†	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection†	[redacted]	5 (2.3)	[redacted]	2 (1)
Alanine aminotransferase increased†	[redacted]	[redacted]	[redacted]	[redacted]
Intestinal obstruction†	[redacted]	10 (4.6)	[redacted]	5 (2.6)
Stomatitis†	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia†	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension†	[redacted]	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased†	[redacted]	[redacted]	[redacted]	[redacted]
Cancer pain†	[redacted]	5 (2.3)	[redacted]	1 (0.5)
Hypocalcaemia†	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism†	[redacted]	3 (1.4)	[redacted]	9 (4.7)

Preferred term	Enco with cetuximab N=216		Control N=193	
	All grades n (%)	Grade 3+ n (%)	All grades n (%)	Grade 3+ n (%)
Small intestinal obstruction†	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia†	[redacted]	[redacted]	[redacted]	[redacted]
Subileus†	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration†	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased†	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased†	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia†	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.
Preferred terms are presented by descending order of frequency in the Enco with cetuximab all grades column down to 10% incidence. For all additional AEs, their presentation is determined by AEs (any grade) that occurred in the control arm ≥10% or any Grade 3+ AE that occurred in either arm at ≥2%.
†Denotes AEs that occur at a rate of ≥2% in any treatment arm for Grade 3+ but at <10% in any treatment arm for all grades.
Source: August update Table 14.3.1-1.3.1 (50).

Table 17 presents a summary of serious AEs, regardless of relationship to study drug, by preferred term, treatment and severity (all grades and maximum Grade 3+).

- The most frequently reported serious AEs (>2.0% of patients) by preferred term:
  - **In the Enco with cetuximab arm:** were intestinal obstruction [redacted], abdominal pain, urinary tract infection and cancer pain [redacted] each);
  - **In the control arm**: were diarrhoea [redacted], intestinal obstruction [redacted], pulmonary embolism and febrile neutropenia [redacted] each), vomiting, abdominal pain, ileus, small intestinal obstruction and subileus [redacted] each).

Table 17: Serious AEs, regardless of relationship to study drug, by preferred term – overall and Grades 3+ (>1% in any treatment arm) – Safety set, data cut-off 15th August 2019

Preferred Term	Enco with cetuximab N=216		Control N=193	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any Serious Adverse Event	[redacted]	[redacted]	[redacted]	[redacted]
Intestinal obstruction	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Cancer pain	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Ileus	[redacted]	[redacted]	[redacted]	[redacted]
Large intestinal obstruction	[redacted]	[redacted]	[redacted]	[redacted]

Preferred Term	Enco with cetuximab N=216		Control N=193	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Small intestinal obstruction	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]
Bile duct obstruction	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]
Malignant melanoma	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Subileus	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]
Large intestine perforation	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]
General physical health deterioration	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.
Preferred terms are presented by descending order of frequency in the Enco with cetuximab all grades column, followed by any additional AEs (all grades) that occurred in the control arm ≥1%.
Source: August update Table 14.3.1-1.8.1 (50).

B.2.11.2 Safety overview

Safety data collected during the Phase 3 randomised portion of the BEACON CRC study (data cut-off 15th August 2019) suggests that the double combination of Enco with cetuximab offers a toxicity and tolerability profile that is favourable compared with investigators choice of chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab):

- Overall, despite duration of exposure in the Enco with cetuximab arm being 2.7 times that in the control arm (K-M estimates: [redacted] weeks), the toxicity profile in terms of overall incidence of AEs ([redacted]% and [redacted]%), Grade 3+ AEs ([redacted] and [redacted]%) and serious AEs ([redacted] vs [redacted]%) was similar or more favourable.

- Comparative incidence rates of specific AEs (all grades) were variable, with some occurring at a higher rate with Enco with cetuximab and others at a lower rate; however, AEs were generally well tolerated and manageable in the Enco with cetuximab arm, with the majority being mild or moderate (Grade 1/2) and Grade 3+ AEs (AEs requiring hospitalisation or prolongation of hospitalisation, AEs that are life threatening or AEs that lead to death) occurring at lower rates than in the control arm in most cases. For example, there was only one Grade 3+ AE reported in >5.0% of patients in the Enco with cetuximab arm (anaemia [redacted]), while those occurring at >5% in the control arm included diarrhoea (10.4%), neutropenia [redacted], neutrophil count decreased [redacted], anaemia [redacted], and, abdominal pain (5.2%), asthenia (5.2%).
- Similarly AEs in the Enco with cetuximab arm had less of an impact on study drug modification or discontinuation than the control arm, with lower rates of AEs leading to dose interruption ([redacted]), dose reduction ([redacted]), any study drug discontinuation ([redacted]), and discontinuation of all study drugs ([redacted]). Accordingly, higher median RDIs were maintained for Enco with cetuximab (Enco, [redacted]%; cetuximab, [redacted]% vs cetuximab, [redacted]%; irinotecan, [redacted]%; 5-fluorouracil, [redacted]%; folinic acid, [redacted]% for component drugs in the Enco with cetuximab and control arms, respectively).
- Moreover, comparison of the two arms across PRO analyses showed a better preservation in QoL for Enco with cetuximab than the control arm (See Section B.2.7.6), suggesting that, overall, the safety profile of Enco with cetuximab was generally more favourable and did not lead to a meaningful impact on QoL.

Conclusion

- The safety profile of the double combination of Enco with cetuximab for patients with previously treated BRAF-mutant mCRC was consistent with the known safety profile for encorafenib (original marketing authorisation for BRAF-mutant melanoma; see SmPC Appendix C), but also for cetuximab.
- Overall, Enco with cetuximab offers patients the choice of a more effective treatment with a favourable toxicity and tolerability profile versus chemotherapy treatments for mCRC (FOLFIRI with cetuximab or irinotecan with cetuximab), as utilised in the BEACON CRC control arm. This is reflected in rates of overall and

individual Grade 3+ AEs that were generally lower with Enco with cetuximab, fewer dose modifications and drug discontinuations.

B.2.12 Ongoing studies

There are no further analyses anticipated from BEACON CRC in the 12 months post-submission.

B.2.13 Innovation

In mCRC with BRAF V600E mutation, patient prognosis is significantly worse than for patients who present without these mutations, and patient survival is dramatically shortened (27, 42). Perversely, there are currently no treatments available that are specifically directed at treating BRAF-mutant mCRC, and standard clinical practice is limited to those treatments used in RAS wild-type disease. However, evidence supporting the effectiveness of such treatments in BRAF-mutant populations is restricted to small subgroup analyses within trials (See Section B.2.10.2) which show limited benefit, with an OS of approximately 4 to 6 months reported (Table 18).

Table 18: Comparison of outcomes in selected studies reporting BRAF-mutant mCRC populations

Study/ reference	Line of therapy	Intervention	N	Median OS (months)
BEACON CRC †	≥2	FOLFIRI with cetuximab or irinotecan with cetuximab	221	5.88
20050181 (42)	2	FOLFIRI	45‡	5.7
RAISE (28)	2	FOLFIRI + placebo	21	4.2
VELOUR (43)	2	FOLFIRI + placebo	36‡	5.5

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; FOLFIRI, folinic acid/fluorouracil/irinotecan; NR, not reported; OS, overall survival.
† BEACON CRC data presented are for the August data cut-off as presented in Form B, Section B.2.7; ‡ N is for overall BRAF-mutant subgroup treated across two treatment arms.

Enco in combination with cetuximab will provide patients and clinicians with a **first-in-class** oral[i] and chemotherapy-free targeted therapy for BRAF V600E-mutant mCRC patients who have received prior systemic therapy. This combination regimen will provide a step change in the treatment of BRAF-mutant mCRC, being the first and only therapy to show demonstrable significant improvement in OS, PFS, and HRQoL, alongside a

[i] Encorafenib is taken orally; cetuximab is taken as an IV infusion.

favourable safety profile in this specific patient group versus standard of care treatments in a Phase 3 clinical trial specifically designed for this population.

The Enco with cetuximab regimen also provides a chemotherapy-free regimen thus minimising the need for intravenous administration. For the new targeted regimen, encorafenib is taken orally once a day (See SmPC, Appendix C) and, based on NHSE guidance and clinical practice, cetuximab requires intravenous infusion over 1–2 hours, every two weeks (5). In comparison, the current second-line chemotherapy regimen of FOLFIRI is much more intensive consisting of three individual drugs (Folinic acid, fluorouracil and irinotecan), each taken intravenously, every two weeks, with infusions being taken sequentially and lasting 2 days (68-70).[j]

By eliminating the need for chemotherapy drugs, the encorafenib regimen also minimises debilitating adverse events that are commonly associated with FOLFIRI and trifluridine-tipiracil, including diarrhoea and febrile neutropenia (68-71).

Overall, the availability of BRAF-targeted therapy with encorafenib, in combination with cetuximab will provide a considerable step change in the treatment of BRAF-mutant mCRC, offering patients the choice of a new therapy which is the first to show demonstrable significant improvement in OS, PFS, and HRQoL, alongside a favourable safety profile in a Phase 3 clinical trial specifically designed for this population.

[j] Trifluridine-tipiracil is administered orally (71).

B.2.14 Interpretation of clinical effectiveness and safety evidence

B.2.14.1 Principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology

For patients with a very poor prognosis, Enco with cetuximab provides a highly needed treatment specifically targeted to BRAF-mutant mCRC

BRAF-mutant mCRC represents an extremely challenging disease state to treat, with the prognosis being so much worse than for patients who present without BRAF mutations; risk of mortality is more than doubled versus BRAF wild-type (27).

There are currently no treatments available which are specifically directed at the BRAF-mutation, and because CRC mutations in BRAF and those of another signalling protein, RAS, are mutually exclusive (25), patients with BRAF V600E-mutant mCRC have been treated to date with standard of care regimens for RAS wild-type mCRC. In the absence of specific treatments for BRAF V600E-mutant mCRC, standard second-line therapies currently provide limited benefit, with an OS of approximately 4 to 6 months reported (28, 42-44). These rates are substantially lower than observed in BRAF wild-type disease (e.g. median OS 4.2 months in BRAF-mutant mCRC vs 15.5 months in RAS/BRAF wild-type for FOLFIRI at second-line (28)).

Given the very poor prognosis for patients with BRAF V600E-mutant mCRC and the lack of a BRAF-mutant specific treatment, there is a clear unmet need in this patient population. Approval of Enco with cetuximab will provide patients and clinicians with a first-in-class oral[k] and chemotherapy-free targeted therapy for BRAF V600E-mutant mCRC patients who have received prior systemic therapy.

BEACON CRC is the first and only Phase 3 RCT designed specifically for patients with BRAF V600E-mutant mCRC, whose disease had progressed after one or two prior regimens in the metastatic setting. The trial is a global, multicentre, randomised, open-label, active controlled trial which provides pivotal efficacy, HRQoL and safety evidence to support the use of encorafenib in combination with cetuximab (Enco with cetuximab; N=220) in the NHS. The control arm comprised investigator's choice of chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab (control arm; N=221). A third arm assessing triple combination of encorafenib and binimetinib with cetuximab (Enco+Bini

[k] Encorafenib is taken orally; cetuximab is taken as an IV infusion.

with cetuximab; N=224) was also included in the trial; results from this arm are no longer relevant to decision making in England since marketing authorisation for the triple combination is not being sought at this time.

Overall, based on the most mature dataset available (August 2019), BEACON CRC showed that the use of targeted therapy with encorafenib, in combination with cetuximab significantly improved OS, PFS and ORR compared with standard of care therapies. This is combined with a favourable safety and tolerability profile and sustained HRQoL.

Targeted therapy of Enco with cetuximab significantly improves OS, ORR and PFS, while sustaining HRQoL versus standard of care therapies

Enco with cetuximab resulted in a 39% reduction in the risk of death equating to a clinically meaningful 3.4 additional months of survival[l] compared with the control arm – median OS 9.30 months vs 5.88 months; HR: 0.61; 95% CI: 0.48, 0.77; one-sided p<0.0001. Multivariate Cox regression stratified by study strata (ECOG PS, prior irinotecan use and cetuximab source) and adjusted for pre-specified baseline covariates provided consistent results ([redacted]) (Section B.2.7.1).

The significant OS improvement observed with this new targeted therapy meet NICE end-of-life criteria (life expectancy with current treatments <24 months and additional survival of >3 months) and represents a substantial step forward for the treatment options available for this patient group (Section B.2.14.3).

The risk of disease progression or death (assessed by blinded central review) was significantly reduced by 56% following Enco with cetuximab therapy – Median PFS 4.27 months vs 1.54 months for control; HR: 0.44; 95% CI: 0.35, 0.55; one-sided p<0.0001. Local assessment of PFS led to similar results. A significantly higher rate of complete or partial response (ORR) was also observed compared with the control arm – 19.5% vs 1.8%; one-sided p<0.0001) (Section B.2.7.2 and B.2.7.3).

HRQoL findings across a number of disease-specific and generic patient-reported tools were consistent with the observation of clinical benefit and favourable toxicity and tolerability of Enco with cetuximab compared with control. Enco with cetuximab substantially delayed deterioration in HRQoL by approximately [redacted] months, as measured

[l] In CRC, ASCO recommend an increase in OS between 3–5 months and a HR of 0.67 translate into a clinically meaningful benefit (54).

by median time to definitive 10% deterioration in the EORTC QLQ-C30 domain scores, FACT-C domain scores and EQ-5D-5L VAS and utility index scores (Section B.2.7.6).

Indirect treatment comparisons support a conclusion of superior efficacy of Enco with cetuximab versus FOLFIRI

Based on the limited evidence available for FOLFIRI in BRAF-mutant populations ITC analyses were performed versus the BEACON CRC study (Section B.2.10).

In these analyses the BEACON CRC control arm was used to link the encorafenib regimen to FOLFIRI. The results showed that Enco with cetuximab is associated with a statistically significant lower hazard of death (OS) and progression (PFS) compared with FOLFIRI.

An ITC was not possible versus trifluridine-tipiracil due to a complete absence of data in the BRAF-mutant mCRC population. A naïve comparison is possible using data for a population of patients for whom BRAF status was not defined but is subject to greater uncertainty than an ITC.

Enco with cetuximab provides a more favourable toxicity and tolerability profile versus standard of care therapies

Safety data collected during the BEACON CRC study (data cut-off August 2019) showed the double combination of Enco with cetuximab in previously treated BRAF-mutant mCRC to be consistent with the known safety profile for encorafenib (original marketing authorisation for BRAF-mutant melanoma; see SmPC Appendix C (Section B.2.11).

Furthermore, the safety data from BEACON CRC suggests that Enco with cetuximab can offer a toxicity and tolerability profile that is more favourable compared with investigators choice of chemotherapy treatments (FOLFIRI or irinotecan) in combination with cetuximab. This is reflected in rates of overall and individual Grade 3+ AEs that were generally lower with Enco with cetuximab, fewer dose modifications and drug discontinuations, and median RDIs that were close to optimal ([redacted]%), as summarised below:

- Despite duration of exposure in the Enco with cetuximab arm being 2.7 times that in the control arm, the toxicity profile in terms of overall incidence of AEs ([redacted]% and [redacted]%), Grade 3+ AEs ([redacted] and [redacted]%) and serious AEs ([redacted] vs [redacted]%) was similar or more favourable.
- Comparative incidence rates of specific AEs (all grades) were variable, with some occurring at a higher rate with Enco with cetuximab and others at a lower rate; however, AEs were generally well tolerated and manageable in the Enco with

cetuximab arm, with the majority being mild or moderate (Grade 1/2) and Grade 3+ AEs (AEs requiring hospitalisation or prolongation of hospitalisation, AEs that are life threatening or AEs that lead to death) occurring at lower rates than in the control arm in most cases. For example, there was only one Grade 3+ AE reported in >5.0% of patients in the Enco with cetuximab arm (anaemia [redacted]), while those occurring at >5% in the control arm included diarrhoea (10.4%), neutropenia [redacted], neutrophil count decreased [redacted], anaemia [redacted], and, abdominal pain (5.2%), asthenia (5.2%).

- AEs in the Enco with cetuximab arm had less of an impact on study drug modification or discontinuation than the control arm, with lower rates of AEs leading to dose interruption ([redacted]), dose reduction ([redacted]), any study drug discontinuation ([redacted]), and discontinuation of all study drugs ([redacted]). Accordingly, higher median RDIs were maintained for Enco with cetuximab (Enco, [redacted]%; cetuximab, [redacted]% vs cetuximab, [redacted]%; irinotecan, [redacted]%; 5-fluorouracil, [redacted]%; folinic acid, [redacted]% for component drugs in the Enco with cetuximab and control arms, respectively).
- Moreover, comparison of the two arms across PRO analyses showed a better preservation in QoL for Enco with cetuximab than the control arm, suggesting that, overall, the safety profile of Enco with cetuximab was generally more favourable and did not lead to a meaningful impact on QoL.

Conclusion

- BEACON CRC is the first and only Phase 3 RCT designed specifically for patients with BRAF V600E-mutant mCRC, whose disease had progressed after one or two prior regimens in the metastatic setting.
- The use of targeted therapy with encorafenib, in combination with cetuximab offers patients the choice of a more effective treatment in terms of OS, PFS and ORR, combined with a more favourable toxicity and tolerability profile and sustained HRQoL compared with chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab, as utilised in the BEACON CRC control arm.
- The significant OS improvements observed with this new targeted therapy meet NICE end-of-life criteria and represent a substantial step forward in the treatment options available for this patient group, whose prognosis can be extremely poor.

B.2.14.2 Strengths and limitations of the clinical evidence base for the technology

B.2.14.2.1 Internal

B.2.14.2.1.1 Study design

BEACON CRC is the first and only Phase 3 RCT designed specifically to assess the effectiveness of a treatment for patients with BRAF V600E-mutant mCRC, whose disease had progressed after one or two prior regimens in the metastatic setting. The study was a large, global, multicentre, active-controlled trial, well-conducted and methodologically robust study. An open-label design was chosen due to the use of both oral and IV study drugs in the study, the characteristic chemotherapy toxicities in the control arm and the characteristic MEK-inhibitor toxicities associated with binimetinib in the Enco+Bini with cetuximab arm that would result in patients being functionally unblinded.

As described in EMA guidelines, the impracticality of employing a double-blind design due to differences in toxicity between study regimens is a frequent situation in oncology trials, and the choice of study endpoints, conduct of sensitivity analyses and independent review are recognised to limit potential bias related to the open-label nature of the trial (72).

Precautions were taken, however, to minimise potential bias including:

- The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a computerised central randomisation list using the IWRS;
- Blinded central review was used for the primary analyses of PFS and response outcomes. The independent central review was blinded to patient treatment assignment throughout its operation. Furthermore, the open-label design is unlikely to yield biased results for OS, as OS is based on objective, all-cause mortality events (73);
- A limited number of study personnel were not blinded to individual treatment assignments for purposes of study conduct (for example site monitoring, data management, patient emergencies or for regulatory reporting purposes) but these personnel did not have access to unblinded aggregate summaries of data.
- Patients who were classified by a local laboratory test as having BRAF wild-type tumours were not excluded from Molecular Pre-screening or Screening. Subsequent

screening using the central laboratory test was encouraged, particularly where clinicopathological features were consistent with a BRAF V600E mutation.

These steps were to remain in place until database lock. The Sponsor was to remain blinded to aggregate OS results until the Enco+Bini with cetuximab arm versus control arm OS endpoint exceeded the superiority boundary or the study was stopped for futility.

B.2.14.2.1.2 Statistical testing

Given the inclusion of multiple treatment arms and endpoints, a hierarchical testing procedure was adopted for statistical testing of the primary and selected secondary efficacy endpoints in BEACON CRC, to control for Type-1 error (alpha). Primary efficacy endpoints were planned for the triple combination of Enco+Bini with cetuximab versus control; however, marketing authorisation for the triple combination is not being sought at this time and results have not been presented. Although the efficacy of the anticipated licensed double regimen of Enco with cetuximab compared with the control arm was assessed under a number of secondary endpoints, these endpoints – OS, PFS and ORR – were all formally tested under the hierarchical testing procedure (see Section B.2.5.2).

B.2.14.2.1.3 Patient characteristics

BEACON CRC trial arms of relevance (Enco with cetuximab and control) were generally well-balanced for patient and disease characteristics, although some imbalances were observed. A higher percentage of patients in the Enco with cetuximab arm were male (52.3% vs 42.5%) and a lower proportion were Asian (11.4% vs 17.6%) versus control. A lower proportion of patients in Enco with cetuximab arm had baseline levels of the tumour marker CEA >5 µg/L (69.5% vs 80.5%).

Sub-group analyses showed OS and PFS results to be generally similar to analyses in the overall trial population in terms of direction of effect (Enco with cetuximab more efficacious than control for OS and PFS). A small number of analyses generated non-significant results with the upper bound of the 95% CI for the HR crossing 1 or the point estimate numerically favouring control, although many were hampered by relatively small numbers. Race (Asian vs non-Asian), gender and CEA at baseline were all consistently in favour of Enco with cetuximab.

B.2.14.2.2 External

B.2.14.2.2.1 Relevance of intervention investigated to anticipated use in clinical practice

The evidence base for Enco with cetuximab from the BEACON CRC trial reflects the anticipated licensed indication and the anticipated use of this treatment in clinical practice in the UK. Trial dosing for encorafenib (300 mg QD) matches the recommended dosing in the (draft) SmPC.

No major factors relating to the BEACON CRC trial have been identified which would likely impact on the applicability of the evidence to adult patients with BRAF V600E-mutant mCRC who have received prior systemic therapy.

B.2.14.2.2.2 Trial populations compared with clinical practice

The BEACON CRC study was a multinational study, 221 clinical sites in 28 countries: 111 sites in Europe, 36 sites in North America and 74 sites in selected countries from the rest of the world. A total of 31 patients from 5 UK sites were randomised.

The population enrolled – adults with BRAF V600E mutant mCRC who have received prior systemic therapy – is consistent with the anticipated indication anticipated licensed indication and the anticipated use of this treatment in clinical practice in the UK. Patient demographics and characteristics at trial baseline are considered to be generally reflective of the patient population expected in clinical practice.

As described in Section B.2.4.11, BEACON enrolled 52.8% females, with a median age of 61 years (Range 26–91 years). Almost all patients were ECOG PS 0-1 (in line with eligibility criteria) and 53.4% of primary tumours were in the right colon. Approximately half of patients had at least 3 organs affected, with the most common site of metastasis being the liver (61.1%) and with lung, lymph nodes and peritoneum/omentum also being affected. The majority (56.8%) had had complete resection of the primary tumour

Information relating to patient characteristics for BRAF-mutant mCRC in the UK is limited by sample size. A 2018 case control study (patients enrolled 2010–2014) who had been identified from the Royal Marsden Hospital (RMH) molecular diagnostic service provides information on 503 patients tested for BRAF mutation between 2010 and 2014, of whom 59 had BRAF mutations and 43 of these had metastatic disease (24).

This small BRAF-mutant mCRC population from UK clinical practice was 63% female with a median age of 70 (Range 29–85 years). The high age in both the trial and this UK dataset is consistent with the observation from Cancer Research UK that colorectal cancer incidence peaks in older age (13). Disease characteristics were generally well-matched between the trial and this UK population although comparison is limited by sample size of the real-world dataset; the real-world UK sample was predominantly ECOG PS 0 or 1 (81%), 51% had their primary tumour on the right side of the bowel, metastatic sites ranged predominantly across liver (42%), peritoneum (54%) and lung (21%), 40% had metastasis at 2 or more sites, and 74% had had resection of the primary tumour (24).

B.2.14.2.2.3 BEACON CRC control arm

The control arm of BEACON CRC comprised investigator's choice of chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab for this group of patients whose mCRC disease had progressed following prior systemic therapy. FOLFIRI represents one of the therapies identified as a comparator for Enco with cetuximab in the NICE scope for this appraisal (see Table 1). Although NICE guidance in non-BRAF-mutant populations prevents the use of cetuximab in this setting (i.e. second-line and beyond) in England (see Section B.1.3.2.1), the choice of FOLFIRI or irinotecan in combination with cetuximab as the BEACON CRC control arm represented the most frequently used therapeutic options among second- or third-line therapies at the time of study initiation in global terms, consistent with European and US guidelines (European Society for Medical Oncology and National Comprehensive Cancer Network) (17, 46).

B.2.14.2.2.4 Comparison of evidence with NICE comparators

Enco with cetuximab

BEACON CRC is the first and only Phase 3 RCT designed specifically for patients with BRAF V600E-mutant mCRC, whose disease had progressed after one or two prior regimens in the metastatic setting. In contrast, patients with BRAF V600E-mutant mCRC patients have been treated to date with standard of care regimens for RAS wild-type mCRC, and there is only limited evidence of treatment benefit for these therapies in BRAF V600E-mutant mCRC. The systematic literature review presented in this submission found only three RCTs, including BEACON CRC, that have been conducted specifically in a BRAF-mutant population, with BEACON CRC being the only Phase 3 study providing evidence for interventions of relevance to the NICE scope. Other evidence for active interventions included in the NICE scope are either limited to RCTs in which BRAF-mutant

population subgroup analyses have been conducted in small samples (FOLFIRI) or evidence is absent (trifluridine-tipiracil) (See ITC, Section B.2.10.2).

In this context BEACON CRC not only provides pivotal evidence to assess the effectiveness of Enco with cetuximab in this setting but also the most robust and comprehensive evidence base for any treatment available to treat this specific patient population.

The results from BEACON CRC show significant benefits of Enco when taken in combination with the EGFR inhibitor, cetuximab, with median OS and PFS estimates of 9.30 months and 4.27 months, respectively. By contrast treatment with investigator's choice of chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab resulted in OS and PFS estimates of 5.88 months and 1.54 months, respectively. Not only do these results demonstrate statistically and clinically significant improvement with the encorafenib regimen but also shows the control arm to be performing as expected for BRAF-mutant mCRC at this line of treatment (second-line and beyond); a number of studies have demonstrated OS ranging between 4.2 and 5.7 months for FOLFIRI based on small sample BRAF-mutant subgroups examined in post first-line settings (28, 42, 43). As described in Section B.2.10.2.4 it is reasonable to assume that the EGFR inhibitors – cetuximab and panitumumab – would be equivalent in their effectiveness.

Comparison with FOLFIRI

Interpretation of the results from BEACON CRC and subsequent comparison with the NICE scope comparator, FOLFIRI can be reasonably achieved in two ways:

1. **Use the BEACON CRC control arm as a proxy for FOLFIRI effectiveness**

Since BEACON CRC is the only Phase 3 RCT specifically investigating the BRAF V600E-mutant mCRC population in a large sample size (N=441 across relevant arms) and given the general paucity of data from RCTs and observational studies for FOLFIRI specifically in BRAF-mutant mCRC populations, BEACON CRC could be considered as the most robust evidence source for estimating the relative effectiveness of Enco with cetuximab.

However, the control arm comprised investigator's choice of FOLFIRI or irinotecan taken in combination with cetuximab. The presence of cetuximab means that the control arm is not directly applicable to inform estimates of relative effectiveness between Enco with cetuximab and FOLFIRI alone, and it is unclear how much benefit cetuximab provides to the overall regimen, although expert opinion (see Table 1 footnote "a") suggests the

benefit of cetuximab could be small. Based on limited empirical evidence within the BRAF-mutant subgroup, median OS estimates with FOLFIRI alone in small BRAF-mutant subgroups range between 4.2 and 5.7 months (Table 18), whereas the control arm of BEACON CRC, where cetuximab is used, provides a slightly longer median OS of 5.88 months. In this context, although the BEACON CRC study may provide a robust evidence source, the inclusion of cetuximab in the control arm may lead to an overestimation of the effect of FOLFIRI when taken without cetuximab and therefore underestimate the additional benefit seen with the encorafenib regimen.

2. Use the ITC to map FOLFIRI evidence with BEACON CRC

Mapping all the available RCT and observational evidence for BRAF-mutant mCRC allowed an ITC to be performed comparing the encorafenib regimen with FOLFIRI (See Section B.2.10). The ITC is subject to some limitations including: having to assume that EGFR inhibitors are equivalent (cetuximab = panitumumab) to allow network to be formed; outcome estimates for FOLFIRI only available from a small post-hoc subgroup analysis (N=45); baseline characteristics only available for the overall trial population for the FOLFIRI study and hence conclusions of comparability specifically between BRAF-mutant populations cannot be made with certainty (See Section B.2.10.2.4).

However, in contrast to the BEACON CRC study where cetuximab was included in the FOLFIRI/irinotecan control arm, the main strength of the ITC was that it allowed evidence for FOLFIRI when administered alone to be incorporated into the evidence network. In this context and with the limitations of the analysis also being considered, the ITC represents the best available evidence to estimate the relative effectiveness of the encorafenib regimen versus FOLFIRI, using a validated statistical approach.

As such, the ITC result is used in the base-case cost-effectiveness analysis. The impact of using the BEACON CRC control arm as a proxy for FOLFIRI effectiveness is explored as a scenario analysis.

Comparison with trifluridine-tipiracil

The systematic literature reviews did not identify any studies that reported data for trifluridine-tipiracil in populations or subpopulations of patients with BRAF V600E-mutant mCRC that could be incorporated into an evidence network; for this reason an ITC was not feasible to compare Enco with cetuximab and trifluridine-tipiracil.

Without evidence in a BRAF-mutant population, a Phase 3 study – RECOURSE (Mayer 2015 (66)) – was identified that could inform a naïve comparison with the encorafenib regimen. However, this approach is subject to high levels of uncertainty. The study was conducted in a mixed population of approximately 50% KRAS wild-type and 50% KRAS mutants, and BRAF status was neither reported nor subgroup data presented. Based on a study of BRAF and KRAS wild-type and mutant variants observed in CRC patients (25), it could be estimated that BRAF-mutations may be present in around 5% of that study population. It is recognised that outcomes in BRAF-mutant populations will be substantially worse than in those without such mutations; Peeters 2015 (42) report substantially better HRs [95% CI] for BRAF wild-type versus BRAF-mutant for OS (0.25 [0.18, 0.36]) and PFS (0.28 [0.20, 0.40]) (See Section B.2.10.5 for further information).

Although the RECOURSE study did not provide information on the BRAF status of enrolled patients it did report that 51% had KRAS mutations. It is known that BRAF and KRAS mutations are mutually exclusive (25), while BRAF mutations occur in patients with KRAS wild-type at a ratio of approximately 1:10 (25). Accordingly, it may be estimated that ~5% of patients in the RECOURSE study may have had BRAF-mutations. This is consistent with UK studies which report incidence of BRAF-mutant CRC at around 8% of all CRC cases (23, 24). This suggests that using outcomes directly from the RECOURSE study to estimate the effectiveness of trifluridine-tipiracil in a BRAF-mutant population may significantly overestimate its effectiveness relative to Enco with cetuximab.

In this context, cost-effectiveness analyses (Section B.3) explore the use of effectiveness data taken from Mayer 2015 which are then adjusted using the HRs from Peeters 2015 (42), to account for the poorer prognosis of BRAF-mutant patients.

B.2.14.2.2.5 Relevance of outcomes to general practice

The key efficacy endpoints in BEACON CRC were OS, PFS and ORR.

Overall survival is universally accepted as a direct measure of benefit that is easily and precisely measured by documenting the date of death, and of direct relevance to clinicians and patients when considering the use of life-extending therapies. EMA guidelines on the evaluation of anticancer drugs in trials (72) advise that is the most persuasive outcome of a clinical trial from both a clinical and methodological perspective.

Prolonged PFS is seen in most cases to also be a relevant measures of patient benefit, so long as the magnitude of the treatment effect is sufficiently large to outbalance toxicity and tolerability problems (72). ORR was also included to allow for a more rapid assessment of potential clinical benefit (48).

The impact of treatment on various aspects of HRQoL was assessed using a number of recognised, reliable and validated tools, including FACT-C, EORTC QLQ-C30, EQ-5D-5L and PGIC (74-77). As disease-specific tools, the FACT-C and EORTC QLQ C30 have been designed to capture the impact of colorectal cancer (FACT-C) and more broadly cancer (EORTC QLQW-C30) on the patient's HRQoL. FACT-C captures the impact of general aspects of the condition (applicable to all cancer types), as well as the adverse symptoms that are most prevalent in mCRC patients. In contrast, the EQ-5D-5L is a standardised measure of health utility that provides a single index value for one's health status and is of most relevance to modelling the economic impact of Enco with cetuximab, in line with the NICE reference case (78). The PGIC is a measure of patients' perceptions of change in their symptoms over time that can be used as an anchoring method to determine the minimal clinically important difference for other PROs.

B.2.14.3 End of life

Pierre Fabre believes that Enco with cetuximab for the treatment of patients with BRAF V600E-mutant mCRC who have received prior systemic therapy meets NICE end-of-life criteria, as described in Table 19.

Table 19: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**Life expectancy estimate with standard of care ~4–6 months** As described in Appendix D, Section D.1.1, limited evidence is available for the efficacy of current treatments specifically in the BRAF V600E-mutant mCRC population. Only three RCTs, including BEACON CRC were identified that specifically assessed treatments in a BRAF-mutant mCRC population, with eight others reporting subgroup results for small BRAF V600E-mutant mCRC subpopulations of the overall trial cohort. Data from the BEACON CRC study shows median OS with chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab = 5.88 months. A number of other studies have demonstrated OS ranging between 4.2 and 5.7 months for FOLFIRI alone based on small sample BRAF-mutant	B.2.7.1.1

Criterion	Data available	Reference in submission (section and page number)
	subgroups examined in post first-line settings (28, 42, 43); these further support the limited life expectancy in patients with BRAF-mutant mCRC in a post first-line setting.	
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	**Extension to life with Enco with cetuximab >3 months** The BEACON CRC Phase 3 RCT showed statistically significant improvements in OS in the Enco with cetuximab arm versus the control of chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab. Median OS with encorafenib/cetuximab combination therapy was 9.3 months, equating to an improvement of 3.4 months (one-sided p<0.0001).	B.2.7.1.1

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; (m)CRC, (metastatic) colorectal cancer; FOLFIRI, folinic acid/fluorouracil/irinotecan; OS, overall survival; RCT, randomised controlled trial.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

B.3.1.1 Systematic review

A systematic literature review (SLR) was conducted to identify available economic evidence in mCRC. Full details of the SLR methodology are presented in Appendix G. In total, eight UK cost-effectiveness analyses were identified which reported cost-effectiveness outputs for treatments used in mCRC (79-86). These studies are tabulated in Table 20 and summarised briefly below.

B.3.1.1.1 Line of therapy

Of the eight published analyses, four assessed first-line treatment and four assessed treatments in previously treated populations; the latter represents the line of therapy of interest to this appraisal.

B.3.1.1.2 Interventions

The analyses assessed a range of other treatments although only three considered comparators of relevance to the company decision problem in second or subsequent lines of therapy: trifluridine-tipiracil (vs BSC) (81, 86); FOLFIRI (vs FOLFIRI + aflibercept + irinotecan) (83). These publications supported NICE technology appraisals (TA405 [trifluridine-tipiracil for previously treated mCRC] and TA307 [aflibercept in combination with irinotecan and fluorouracil-based therapy for treating mCRC that has progressed following prior oxaliplatin-based chemotherapy], respectively. Four of the remaining five publications supported NICE TAs of other treatments assessed by NICE for mCRC (80, 82, 84, 85). The remaining study made reference to previous health technology assessment (HTA) economic models for cetuximab and presented a new analysis (79).

B.3.1.1.3 BRAF-mutant populations

None of the studies explicitly stated that BRAF-mutant populations or subpopulations had been considered.

B.3.1.2 NICE technology appraisals

Separately, the NICE website was searched and identified six TAs conducted in mCRC since 2005 which were deemed to be of relevance to the decision problem and which were subsequently interrogated to guide the model structure, parameters and assumptions for

this appraisal (TA118, TA212, TA242, TA307, TA405, TA439 (31, 33-37)[m]). NICE TAs are summarised in Table 22 and referenced as required within specific modelling subsections.

Previous NICE TAs of treatments for mCRC in the UK, along with published cost-effectiveness UK analyses identified in the economic SLR were used to inform the de novo model structure, assumptions and data sources, as described in B.3.2.

[m] Given the large number of TAs conducted in this disease area a date limit was applied which excluded TA61 published in 2003 (32).

Table 20: Overview of UK cost-effectiveness studies

Author/ year	Country/ perspective	Model summary	Study population	Comparison	Trial used as efficacy and safety data source	Incremental QALY (or LYG)	Incremental costs	ICER (per QALY gained)
Untreated/ first-line								
Harty 2018 (79)	UK NHS	• Markov state and transition model with the probabilities of transitions dependent on time from the beginning of treatment of cohort and on time in state • Time horizon: 19 years • Cycle length: week	First-line mCRC	CET + FOLFIRI vs FOLFIRI alone	NR	QALYs: • ITT population: 0.12 • KRAS wild-type cohort: 0.22 • RAS wild-type cohort: 0.35 LY: • ITT population: 0.16 • KRAS wild-type cohort: 0.29 • RAS wild-type cohort: 0.45	• ITT population: £15,802 • KRAS wild-type cohort: £15,907 • RAS wild-type cohort: £15,495	• ITT population: £130,929 • KRAS wild-type cohort: £72,053 • RAS wild-type cohort: £44,185
Tikhonova 2018 (80) Linked to ERG analysis in NICE TA439	UK, • UK NHS • Personal Social Services perspective	• Partitioned survival model • Time horizon: 30 years • Cycle length: 1 month	Previously untreated RAS wild-type (i.e. non-mutated) mCRC, not eligible for liver resection at baseline. All patients are assumed aged 63 years at the start of first-line treatment, with 66% of patients male.	• CET + FOLFOX • PAN + FOLFOX • FOLFOX • CET + FOLFIRI • FOLFIRI • FOLFOX alone or FOLFIRI alone	NR	Without adjustment for subsequent treatment (mean, discounted): • CET+FOLFOX vs. FOLFOX: 0.12 • PAN+FOLFOX vs. FOLFOX: 0.31 • CET+FOLFIRI vs. FOLFIRI: 0.49 With adjustment for subsequent	Without adjustment for subsequent treatment £ (mean, discounted): • CET + FOLFOX vs. FOLFOX: £29,706 • PAN+FOLFOX vs. FOLFOX: £32,797 • CET+FOLFIRI vs. FOLFIRI: £40,947 With adjustment for subsequent	Without adjustment for subsequent treatment (mean, discounted): • CET+FOLFOX vs. FOLFOX: £243,975 • PAN+FOLFOX vs. FOLFOX: £106,276 • CET+FOLFIRI vs. FOLFIRI: £83,168 With adjustment for subsequent treatment (mean, discounted): • PAN+FOLFOX vs. FOLFOX: £86,329 • CET+FOLFIRI vs. FOLFIRI: £68,079

Author/ year	Country/ perspective	Model summary	Study population	Comparison	Trial used as efficacy and safety data source	Incremental QALY (or LYG)	Incremental costs	ICER (per QALY gained)
						treatment (mean, discounted): • PAN+FOLFOX vs. FOLFOX: 0.41 • CET+FOLFIRI vs. FOLFIRI: 0.66	treatment (mean, discounted): • PAN+FOLFOX vs. FOLFOX: £35,094 • CET+FOLFIRI vs. FOLFIRI: £44,849	
Huxley 2017 (82) Linked to ERG analysis in NICE TA439	UK, PenTAG model: NHS and personal social services	PenTAG: de novo cost–utility model • Time horizon: PenTAG cost-effectiveness model: 30 years • Cycle length: PenTAG cost-effectiveness model: 1 month	Population specified in the final NICE scope was people with previously untreated RAS wild-type mCRC We assumed that all patients were aged 63 years at the start of first-line treatment and that 66% were male. The subgroup of interest was based on the location of metastases, specifically liver- and non-liver-limited disease.	• PAN + FOLFOX • CET + FOLFOX • CET + FOLFIRI	• CRYSTAL trial • PRIME trial	FOLFOX network: • CET+FOLFOX vs FOLFOX: 0.12 • PAN+FOLFOX vs FOLFOX: 0.31 FOLFIRI network: • CET+FOLFIRI vs FOLFIRI: 0.49	FOLFOX network: • CET+FOLFOX vs FOLFOX: £26,781 • PAN+FOLFOX vs FOLFOX: £28,572 FOLFIRI network: • CET+FOLFIRI vs FOLFIRI: £41,614	PenTAG model: • FOLFOX network: ICERs per QALY gained compared with FOLFOX – CET plus FOLFOX £104,205, PAN plus FOLFOX £204,103. • FOLFIRI network: ICER per QALY gained compared with FOLFIRI – CET plus FOLFIRI £122,554
Whyte 2012 (85) Linked to ERG analysis in NICE TA212	UK, NR	Time horizon: 8 years (lifetime)	Adult patients with histologically confirmed mCRC who had not previously been treated	• Placebo + XELOX • Placebo + FOLFOX • BEV + XELOX • BEV + FOLFOX	N016966 trial	NR	NR	Without PAS • B-XELOX vs XELOX: £82,098/QALY • B-FOLFOX vs FOLFOX: £94,989/QALY With PAS • B-XELOX vs XELOX: £34,170/QALY

Author/ year	Country/ perspective	Model summary	Study population	Comparison	Trial used as efficacy and safety data source	Incremental QALY (or LYG)	Incremental costs	ICER (per QALY gained)
								• B-FOLFOX vs FOLFOX: £41,388/QALY
Second and subsequent lines/ previously treated								
Ramaekers 2018 (86) Linked to ERG analysis in NICE TA405	UK, NHS	• Partitioned survival model • Time horizon: 10 years • Cycle length: 1 day	Previously treated mCRC	T/T vs BSC	• RECOURSE trial • CORRECT trial	T/T: 0.144	NR	• £52,695 (RECOURSE trial only) • £49,392 (pooled evidence)
Bullement 2018 (81) Linked to NICE TA405	UK, UK NHS	• Partitioned survival cost-utility model • Time horizon: 10 years • Cycle length: 28 days	mCRC previously treated with, or not considered candidates for, standard chemotherapies.	T/T and REGO vs BSC	NR	QALYs: • T/T vs.BSC: 0.17 • REGO vs. BSC: 0.11 • REGO vs. T/T: -0.06 LY: • T/T vs.BSC: 0.26 • REGO vs. BSC: 0.16 • REGO vs. T/T: -0.10	• T/T vs.BSC: £8,479 • REGO vs. BSC: £14,613 • REGO vs. T/T: £6,134	Compared with BSC alone, T/T is associated with incremental QALY gain of 0.17
Wade 2015 (83) Linked to ERG analysis in NICE TA307	UK, NR	• Markov model • Time horizon: 15 years • Cycle length: 2 weeks	Patients with mCRC resistant to or has progressed after an oxaliplatin-containing regimen	• Aflibercept in combination with IRIN and FOLFIRI • FOLFIRI alone	VELOUR trial	NR	NR	Manufacturer's base-case: £36,294 ERG's base-case: £54,368

Author/ year	Country/ perspective	Model summary	Study population	Comparison	Trial used as efficacy and safety data source	Incremental QALY (or LYG)	Incremental costs	ICER (per QALY gained)
Hoyle 2013 (84) Linked to ERG analysis in NICE TA242	UK, NHS and PSS in accordance with the NICE reference case (for PenTAG cost-effectiveness model)	• A decision-analytic model PenTAG • Time horizon: 10 years • Cycle length: 1 month	Adults with mCRC who have failed first-line chemotherapy. This is further restricted to patients with EGFR expressing metastatic colorectal cancer with KRAS wild-type status for CET and PAN in line with the marketing authorisations for these treatments.	From PenTAG's report: • CET + BSC vs BSC • CET + IRIN vs BSC	NR	QALYs: • CET vs BSC: 0.25 • PAN vs BSC: 0.19 • CET+IRIN vs BSC: 0.6 LY: • CET vs BSC: 0.32 • PAN vs BSC: 0.19 • CET+IRIN vs BSC: 0.87	• CET vs BSC: £24,500 • PAN vs BSC: £29,000 • CET+IRIN vs BSC: £53,100	QALYs: • CET compared with best supportive care is £98,000 per QALY gained • PAN compared with best supportive care is £150,000 per QALY gained • CET plus irinotecan compared with best supportive care is £88,000 per QALY gained LY: • CET vs BSC: £78,000 • PAN vs BSC: £145,000 • CET+IRIN vs BSC: £64,000

Abbreviations: BEV, bevacizumb; BSC, best supportive care; CET, cetuximab; (m)CRC, (metastatic) colorectal cancer; ICER, incremental cost-effectiveness ratio; IRIN, irinotecan; ITT, intention-to-treat; KRAS, KRAS proto-oncogene, GTPase; LY, life year; LYG, life year gained; mCRC, metastatic colorectal cancer; FOLFOX, Folinic acid/fluorouracil/oxaliplatin; PAN, panitumumab; PenTAG; Peninsula Technology Assessment Group; QALY, quality-adjusted life year; RAS, RAS family of proto-oncogenes, GTPases; REGO, regorafenib; T/T, trifluridine/tipiracil; XELOX, capecitabine, oxaliplatin.

B.3.2 Economic analysis

None of the CEAs identified in the economic SLR included Enco with cetuximab as a comparator. Therefore, it was necessary to include a de novo economic model in this submission.

The objective of the economic evaluation was to assess the cost-effectiveness of Enco with cetuximab for the treatment of patients with BRAF V600E-mutant mCRC, versus relevant comparators as defined in the company decision problem (See Table 1).

The model perspective is the NHS and personal social services (PSS) in England. The cost-effectiveness analysis is based on clinical data from three main sources, including:

- A grouped treatment nodes ITC (described in Section B.2.10) which generated HRs of relative effect between FOLFIRI and Enco with cetuximab, which were then applied to the BEACON CRC Enco with cetuximab survival curves.
- BEACON CRC trial (described in Section B.2.3), the pivotal Phase 3 study for encorafenib with cetuximab for V600E BRAF-mutant mCRC.
- Digitised K-M curves from a Phase 3 trial of trifluridine-tipiracil to generate an estimate of the trial individual patient data (IPD) (66).

B.3.2.1 Patient population

The economic evaluation includes patients with BRAF V600E-mutant mCRC who have received prior systemic therapy. This is consistent with the NICE scope and company decision problem (see Table 1), the population included in the BEACON study (see Section B.2.3) and with the anticipated European marketing authorisation for Enco with cetuximab in mCRC (See Table 2).

The base-case cohort characteristics reflect the baseline patient characteristics across the entire study population in BEACON CRC, the pivotal Phase 3 RCT for encorafenib (Table 21).

Table 21: Base-case cohort characteristics at baseline

	BEACON CRC	Source
Age (SD)	59.30 (11.80)	BEACON CRC CSR Table 14.1-3.1.1 (48)
BSA (SD)	1.79 (0.23)	
Percentage males	47.2%	

Abbreviations: BSA, body surface area; CSR, clinical study report; SD, standard deviation.

The age and proportion of the cohort who are male are pertinent as they are used to determine age and sex-related utility changes as described in Section B.3.4.5.3. The body surface area (BSA) is used to determine the doses required for drugs which are dosed based on BSA, as described in Section B.3.5.1.1.

B.3.2.2 Model structure

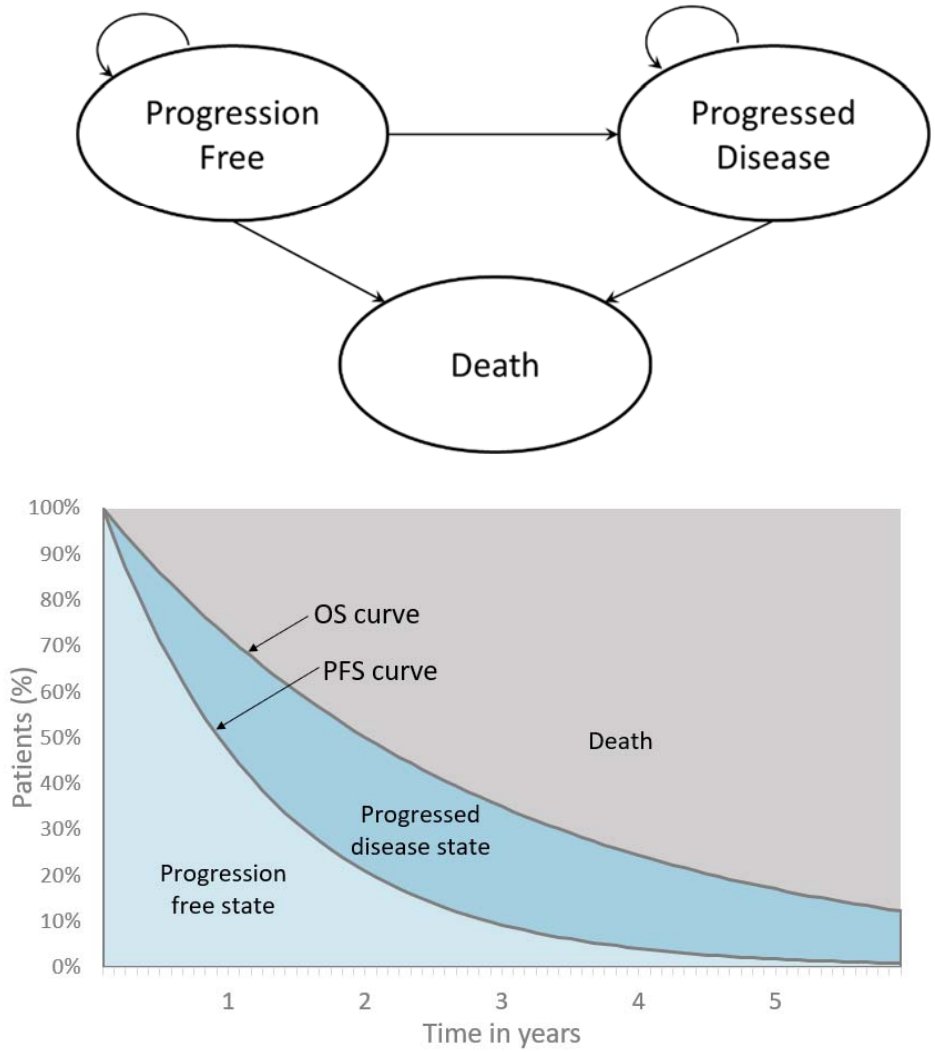
A partitioned survival model with a lifetime horizon was developed to determine the cost-effectiveness of Enco with cetuximab versus relevant comparators as defined in the company decision problem for the treatment of patients with BRAF V600E-mutant mCRC who have received prior systemic therapy. The concept of the model is similar to that used in numerous prior economic evaluations of treatments for advanced or metastatic cancers, including two NICE appraisals for previously treated mCRC (NICE TA405 (31) and NICE TA242 (35)). A summary of all NICE TAs conducted for treatments of mCRC since 2005 is presented in Table 22.

Partitioned survival analysis is the most commonly used modelling approach within NICE HTAs for interventions treating advanced or metastatic cancer (87). The advantages of this approach in this disease are as follows:

- OS and PFS data from the clinical trial can be used directly in the model.
- Time dependencies and treatment effects are reflected within the survival curves (whereas a Markov model, for example, would require cumbersome tunnel states).
- HRs from NMAs can be easily incorporated by applying these to the OS and PFS curves directly.

The current model was developed in Microsoft Excel 2016 and it includes three mutually exclusive health states (Figure 7): pre-progression (or progression-free), post-progression (or progressed disease) and death.

Figure 7: Model structure



Abbreviations: OS, overall survival; PFS, progression-free survival.
Please note that the bottom panel of this chart is purely illustrative and is not based on any efficacy data reported elsewhere in this document.

State membership is determined from a set of non-mutually exclusive survival curves. The cohort enters the model in the pre-progression health state and any transitions to post-progression and death are defined by the PFS and OS curves. The proportion of the cohort remaining in the pre-progression health state over time is derived directly from the PFS curve (Figure 7). State membership for the death state is calculated as 1 minus the OS curve and state membership for the post-progression health state is derived as the difference between the OS and the PFS curve (the proportion of patients who are alive but not pre-progression).

B.3.2.2.1 Time horizon and cycle length

The base-case time horizon is 10 years, which is deemed sufficiently long to represent a life-time horizon and account for all incurred costs and effects (Expert opinion, see Section B.3.3.3). The model has a cycle length of one month (365 days/12 months = 30.42 days per month), which corresponds to a sufficient length of time to account for changes in PFS, OS and time to treatment discontinuation (TTD), and is not too short to impair computational efficiency. The monthly cycle length also aligns with chemotherapy treatment cycle durations, which are usually given in cycles numbered in weeks (e.g. 2 weeks for a cycle of treatment with cetuximab, 2 weeks for FOLFIRI and 4 weeks for trifluridine-tipiracil (5, 68-71)).

Since trial endpoints (OS, PFS) are included in the model based on observation of patients at the end of each month, half cycle correction was used. The need for half cycle correction decreases as cycles get smaller (e.g. one week), however one-month cycles still require this approach to adjust for the uncertainty about the timing of events.

B.3.2.2.2 Perspective and discounting

The base-case analysis takes the perspective of the NHS and PSS in England. Both costs and outcomes (Life years [LYs] and QALYs) were discounted at 3.5%, in line with the NICE guide to the methods of technology appraisal 2013 (88). The discount rate was not varied in the DSA as per the reference case and was not varied in the PSA as it would not be informative.

B.3.2.2.3 Model outcomes

The results of the model are expressed as an incremental cost-effectiveness ratio (ICER), in terms of incremental cost per quality-adjusted life year (QALY) gained and as incremental cost per LY gained. The features of the economic analysis in comparison to previous TAs conducted in this (or similar) disease area are shown in Table 22.

Table 22: Features of the economic analysis in comparison to previous TAs†

Factor	Previous NICE appraisals						Current appraisal	
	TA118 (33)	TA212 (34)	TA242 (35)	TA307 (36)	TA405 (31)	TA439 (37)	Chosen values	Justification
Time horizon	Not explicitly stated; short	8 years	10 years	15 years	10 years	10 years	10 years	Clinical expert feedback (see Section B.3.3.3) based on poor prognosis for mCRC patients with BRAF V600E mutation
Cycle length	One month	One month	One month	Two weeks	One day	One week	One month	Close match to treatment regimen cycles
Model approach	Partitioned survival	Partitioned survival	Partitioned survival (PenTAG)	Partitioned survival, not explicitly stated	Partitioned survival	Semi-Markov	Partitioned survival	Availability of IPD from the BEACON Phase 3 trial
Treatment waning effect?	Not described	Not described	Not described	Not described	Not described	Not described	None assumed	Clinical expert feedback
Source of clinical outcomes data	AVF2107g/ AVF2192g trials	NO16966 study	Mixed treatment comparison	VELOUR trial	Yoshino 2012, RECOURSE	CRYSTAL, FIRE-3, OPUS, Adam 2004	ITC; BEACON CRC; RECOURSE	An ITC was possible alongside analysis of the trial data
Source of utilities	AVF2107g/ AVF2192g trials	TA176	CO.17 trial	mCRC utilities study	CORRECT trial	Bennett 2011, Wang 2011, Petrou and Hockley 2005	BEACON CRC	Utility data were gathered in BEACON CRC directly and are specific to the trial population
Source of costs/ resource use	SLR	BNF/ PSSRU	BNF/ NHS Schedule of Reference Costs	Retrospective observational study, BNF, PSSRU, NHS Schedule of Reference Costs	SLR, BNF, PSSRU, NHS Schedule of Reference Costs	SLR, BNF, PSSRU, NHS Schedule of Reference Costs	SLR, BNF, PSSRU, NHS Schedule of Reference Costs, CMU eMITS, clinical expert feedback	As per the NICE reference case

Abbreviations: BNF, British National Formulary; BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; CMU, Commercial Medicines Unit; eMIT, Electronic market information tool; IPD, individual patient data; ITC, indirect treatment comparison; mCRC, metastatic colorectal cancer; NHS, National Health Service; PenTAG, Peninsula Technology Assessment Group; PSSRU, Personal Social Services Research Unit; SLR, systematic literature review; TA, technology assessment.
†Given the large number of TAs conducted in this disease area a date limit was applied which excluded TA61 published in 2003 (32).

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention included

The intervention in the analysis is Enco with cetuximab as per the company decision problem (see Table 1). The dose of encorafenib (300 mg QD) is consistent with that assessed in the BEACON CRC study (see Section B.2.4.7) and in line with the anticipated European marketing authorisation. The dose of cetuximab is implemented in the model in line with NHS clinical practice (500 mg/m^2 every 2 weeks (5)) in contrast to the BEACON CRC study where this was administered as per the marketing authorisation (250 mg/m^2 once weekly (4)).

B.3.2.3.2 Relevant comparators included

In line with current NHS practice, the comparators assessed include:

- FOLFIRI (folinic acid/fluorouracil/irinotecan)
- Trifluridine-tipiracil

B.3.2.3.3 Comparators not considered

As per the company decision problem, BSC and irinotecan are not considered relevant comparators; see Table 1 for further details.

B.3.3 Clinical parameters and variables

K-M data are limited to the duration of the BEACON CRC trial for PFS, OS and TTD (~22 months), and therefore to estimate the long-term effect associated with Enco with cetuximab, it was necessary to extrapolate beyond trial follow-up. Long-term extrapolations are highly sensitive to the parametric distributions applied and goodness of fit during the trial period may not always be informative with respect to the accuracy of curve projections beyond the follow-up period. To mitigate such concern, several extrapolation approaches were explored, and the extrapolated curves were validated by both clinical and health economic experts (See Section B.3.3.3 for a description of methods used to elicit expert input).

B.3.3.1 PFS, OS and TTD

B.3.3.1.1 Summary

B.3.3.1.1.1 Enco with cetuximab and FOLFIRI

Base-case efficacy for Enco with cetuximab was estimated by utilising IPD from the BEACON CRC trial to generate OS and PFS curves for the Enco with cetuximab arm.

Base-case efficacy for FOLFIRI was estimated by applying OS and PFS HRs to these curves derived from the ITC described in Section B.2.10. Scenario analyses were also conducted for which the BEACON CRC control arm (FOLFIRI or irinotecan in combination with cetuximab) was taken as a proxy for FOLFIRI efficacy.

The rationale for the choice of FOLFIRI efficacy for base-case and scenario analyses is provided in Section B.2.14.2.2.4.

K-M curves were generated using the IPD from BEACON CRC for the following treatment arms:

- Enco with cetuximab
- FOLFIRI (in scenario analyses only; the base-case uses outputs from a grouped nodes ITC to model FOLFIRI efficacy)

OS and PFS curves were first generated for the BEACON CRC IPD from the earlier February 2019 data cut. These were validated against the K-M plots presented in the BEACON CRC CSR (K-M plots presented in Appendix L), which utilised the same data cut-off. When the final August 2019 data cut was analysed, the same methods as were used for the February data cut were applied to the August data to ensure the modelling approach was consistent with that presented in the CSR.

Methods are described further in Section B.3.3.1.2 and B.3.3.1.3.

B.3.3.1.1.2 Trifluridine-tipiracil

Trifluridine-tipiracil was not included as a comparator in BEACON CRC, and an absence of relevant evidence for this comparator in the BRAF-mutant mCRC population meant that an ITC was not feasible to compare trifluridine-tipiracil and Enco with cetuximab. Therefore, based on evidence identified in the clinical SLR (described in Appendix D and Section B.2.10.5) a naïve comparison had to be made against the BEACON CRC trial data. Mayer 2015 (RECOURSE) was identified as the most appropriate trifluridine-tipiracil trial conducted (66). The raw IPD used for this publication were not available, so the K-M plots presented in the trial publication were digitised and the methods described in Guyot 2012 (89) applied to reconstruct an estimate of the IPD using the OS and PFS curves along with their censoring information and number of patients at risk. To adjust for the fact that the RECOURSE population included predominantly BRAF wild-type patients, the generated parametric models fit to the OS and PFS curves were further adjusted by applying HRs for the presence of BRAF-mutations. Methods are described further in Section B.3.3.1.4.

B.3.3.1.1.3 Statistical analysis

All statistical analyses were performed in R (version 3.6.1). K-M curve fitting was performed using the surv package (included with R) and parametric models were fitted using the flexsurv package. Cholesky decompositions of the variance-covariance matrices for model parameters were generated to enable the probabilistic modelling of different survival curves in the PSA. R plots were generated using the ggplot2 package.

When the model parameters were varied in the PSA, the curves for all treatments were generated by using their respective Cholesky decompositions to sample the parameters to be used for the parametric models. The implementation of the Cholesky decompositions can be seen on the “Cholesky” tab of the economic model.

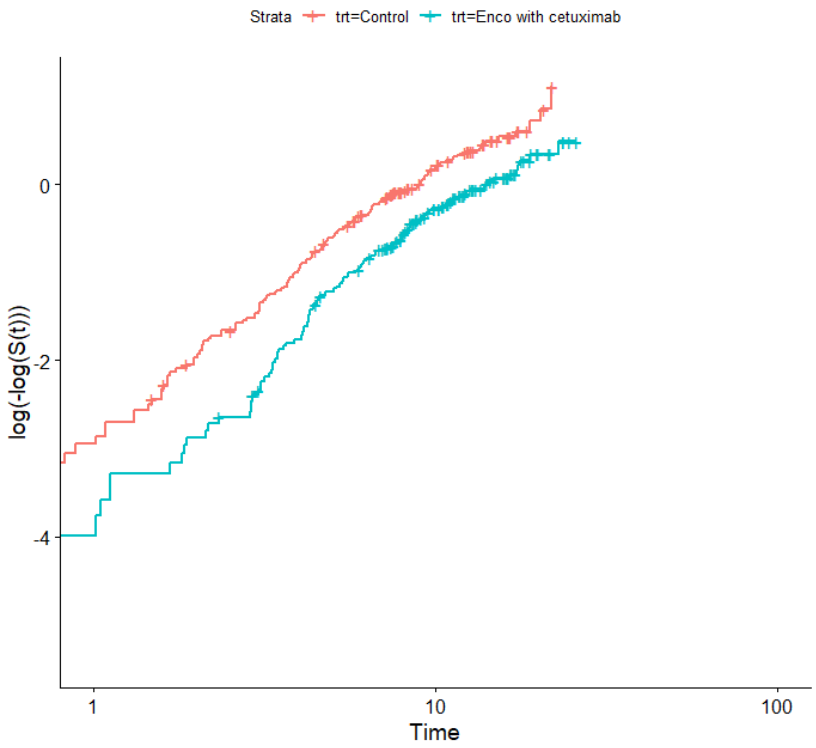
B.3.3.1.1.4 Model selection for OS and PFS

NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 (90) was referred to for the model selection process. The criteria used to determine the parametric model to use for extrapolations of OS, PFS and TTD curves were the following:

- Complementary log-log plots.
- Statistical methods i.e. use of the Akaike information criterion (AIC) and Bayesian information criterion (BIC).
- Expert feedback (visual inspection and clinical validity).

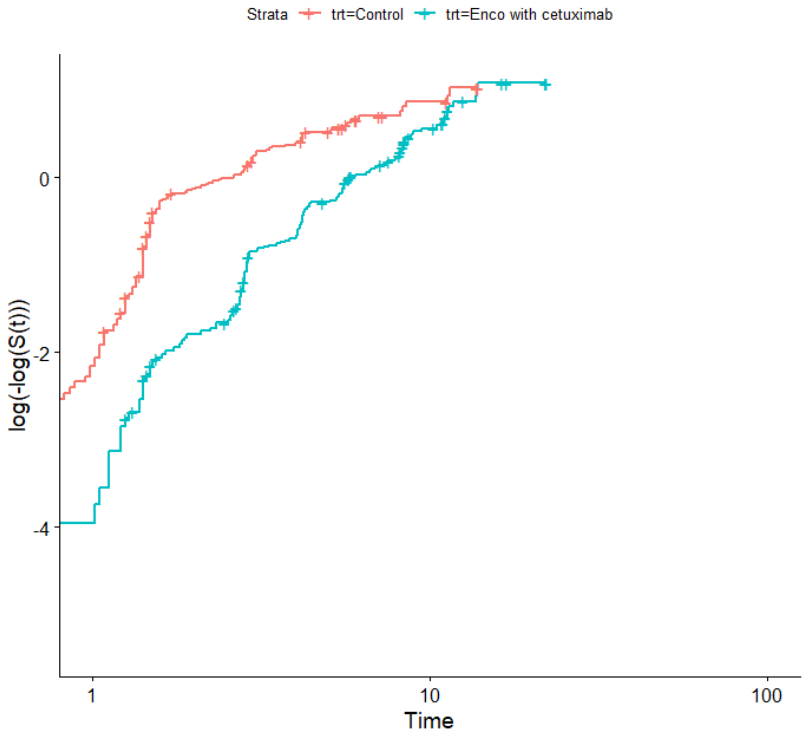
Complementary log-log plots for Enco with cetuximab versus the BEACON CRC control arm are presented in Figure 8 and Figure 9 for OS and PFS, respectively. The proportional hazards assumption appeared to be reasonable for OS as shown by the approximately parallel lines for Enco with cetuximab and the control arm but did not appear to be appropriate for PFS, as the lines for each arm have different gradients. Based on these analyses, to ensure that the modelling approaches were consistent for both OS and PFS, it was determined that the proportional hazards assumption was not appropriate and individual parametric models needed to be fitted to the K-M data.

Figure 8: Complementary log-log plot for Enco with cetuximab versus control arm: OS



Abbreviations: OS, overall survival

Figure 9: Complementary log-log plot for Enco with cetuximab versus control arm: PFS



Abbreviations: PFS, progression-free survival.

To determine the parametric models to be used for extrapolation of survival estimates, the AIC and BIC were considered. A summary of the AIC and BIC statistics for each parametric model across each intervention/ comparator are presented in Table 23. Whilst the ITC was used to estimate the efficacy of FOLFIRI in the base-case analysis, the goodness-of-fit for the control arm of BEACON CRC was considered when choosing the best-fitting parametric model to use across all treatments, as use of the BEACON control arm to estimate the efficacy of FOLFIRI was explored in a scenario analysis.

Table 23: AIC and BIC for parametric models fit to IPD

Arm	Model	OS		PFS	
		AIC	BIC	AIC	BIC
Enco with cetuximab (based on Enco with cetuximab arm from BEACON CRC)	Exponential	946.602	949.995	960.869	964.263
	Generalised gamma	934.049	944.230	924.378	934.559
	Gompertz	946.427	953.215	956.835	963.622
	Loglogistic	929.413	936.201	920.466	927.253
	Lognormal	934.883	941.670	924.196	930.984
	Weibull	937.740	944.527	936.560	943.347
FOLFIRI (based on control from BEACON CRC)	Exponential	1009.823	1013.222	642.595	645.993
	Generalised gamma	1003.563	1013.758	604.080	614.274
	Gompertz	1010.320	1017.117	640.182	646.978
	Loglogistic	1000.316	1007.112	588.566	595.362
	Lognormal	1012.299	1019.095	602.198	608.994
	Weibull	1004.630	1011.426	641.084	647.880
Trifluridine-tipiracil (digitised from Mayer 2015)	Exponential	2438.367	2442.647	2208.645	2212.925
	Generalised gamma	2360.107	2372.948	2001.787	2014.628
	Gompertz	2408.460	2417.020	2206.156	2214.717
	Loglogistic	2353.473	2362.034	2015.747	2024.308
	Lognormal	2371.367	2379.928	2016.782	2025.342
	Weibull	2369.837	2378.398	2147.006	2155.567

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

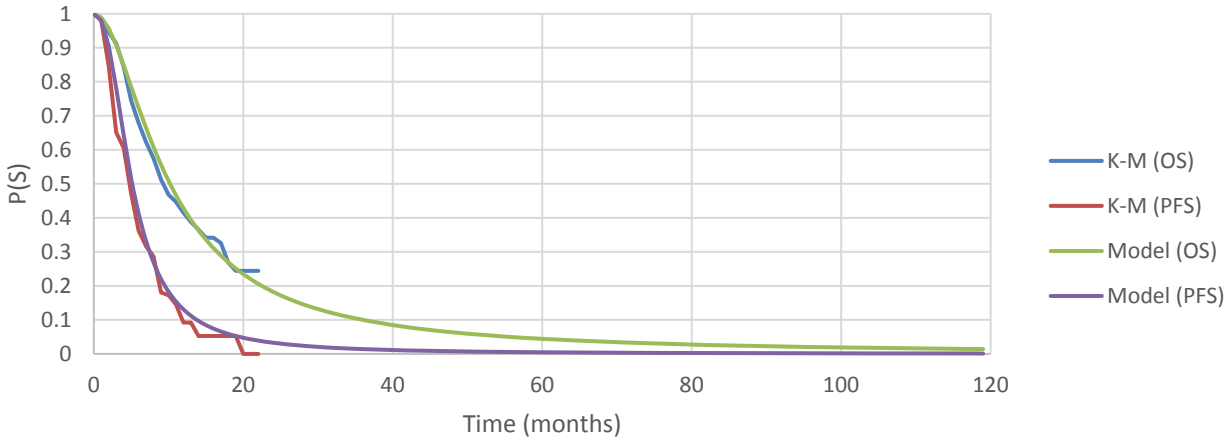
NICE DSU TSD 14 states that the same type of parametric model should be used across treatment arms, i.e. if a loglogistic model is used to model OS in one arm of a trial, then a loglogistic model should be fit to the other arms in the trial as well (90). To determine the optimal models to use, the parametric model with the lowest AIC/BIC across all treatment arms was identified. In this context, the optimal average (across all treatments, for OS and PFS) parametric model identified was the loglogistic model.

Model fits were validated by oncology experts (See Section B.3.3.3) based on visual inspection who stated that the loglogistic and Weibull parametric models provided feasible estimates of long-term survival; opinion was mixed and some experts stated that the Weibull model could generate potentially conservative, albeit plausible estimates of survival based on the poorer prognosis seen in BRAF-mutant patients. However, as the loglogistic parametric model also had the lowest AIC and BIC across all BEACON treatment arms, the loglogistic model was selected for the base-case analysis. The loglogistic model predicted approximately 4% of patients in the Enco with cetuximab arm and 2.4% of patients in the control arm of BEACON were still alive at 60 months. Data from Cancer Research UK suggests that 10.3% of all patients with mCRC would be alive after 60 months (22). After adjusting this survival rate for the poorer prognosis observed with BRAF-mutations (Published HRs for BRAF-mutant vs BRAF wild-type OS: HR 2.24 from Safaee Ardekani meta-analysis of RCTs and cohort studies (27); HR 4.0 from Peeters 2015 (42)) it could be expected that a small proportion of patients on current treatments would still be alive at the 60 month timepoint.

The base-case loglogistic parametric models are shown in Figure 10, Figure 11, Figure 12, and Figure 13. Please note that the K-M lines on each of the plots are K-M estimates derived using the “survest” function in R and not the true K-M curves from the IPD; the IPD-level data were used to generate the models and the K-M curves shown here are purely illustrative.

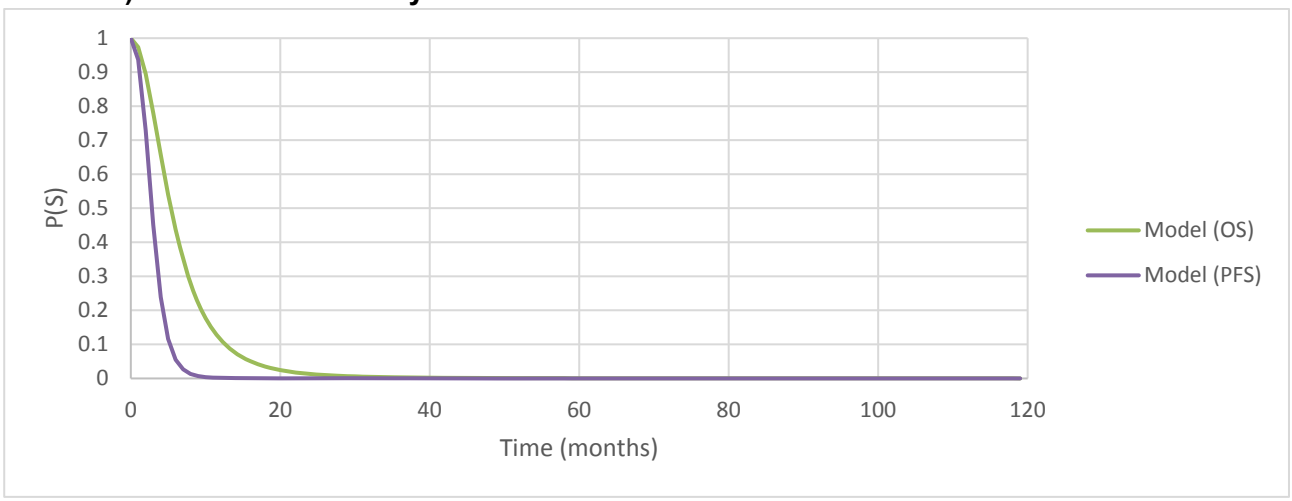
The Weibull models predicted that almost all patients (>99%) had died at 60 months across all treatment arms. Whilst this scenario will likely be a more conservative estimation of effectiveness in that it may be overly pessimistic, it is modelled in a scenario analysis (Section B.3.8.4).

Figure 10: Final model fits for Enco with cetuximab



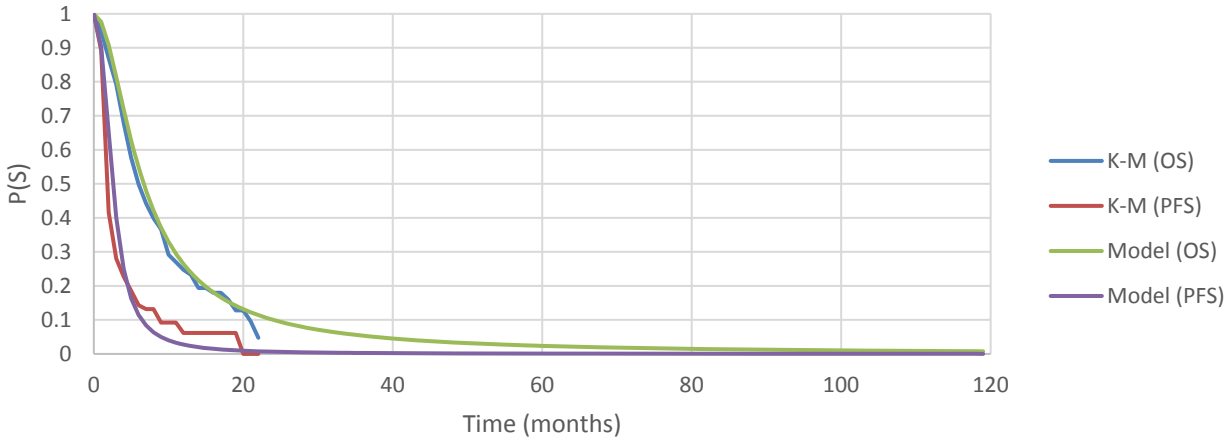
Abbreviations: K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

Figure 11: Final model fits for FOLFIRI (generated from HRs applied to Enco with cetuximab from ITC): for base-case analysis



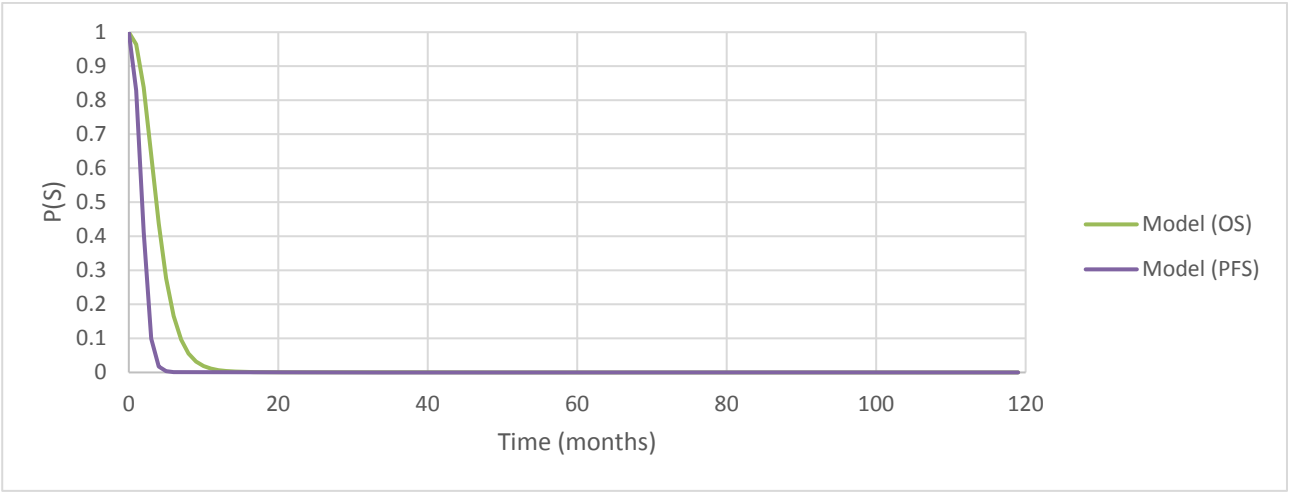
Abbreviations: K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

Figure 12: Final model fits for FOLFIRI (using BEACON CRC IPD): for scenario analysis only



Abbreviations: K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

Figure 13: Final model fits for trifluridine-tipiracil (Mayer 2015, with BRAF mutant mCRC HRs from Peeters 2015 applied)



Abbreviations: K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.
Sources: Mayer 2015 (66); Peeters 2015 (42).

B.3.3.1.2 Enco with cetuximab: BEACON CRC

B.3.3.1.2.1 Parametric model parameters

The parametric model parameters that were fitted to the OS and PFS curves for Enco with cetuximab are shown in Table 24 and Table 25, respectively.

Table 24: Model parameters and goodness-of-fit criteria for Enco with cetuximab from BEACON CRC: OS

Model	AIC	BIC	Parameter	Parameter value
Exponential	946.602	949.995	Intercept	-2.689849986
Generalised gamma	934.049	944.230	Mu	2.426251534
			Sigma	-0.054559809

Model	AIC	BIC	Parameter	Parameter value
			Q	0.396458894
Gompertz	946.427	953.215	Shape	0.026281776
			Rate	-2.852295579
Loglogistic	929.413	936.201	Shape	0.526403902
			Scale	2.270866926
Lognormal	934.883	941.670	Meanlog	2.290600432
			Sdlog	0.067688575
Weibull	937.740	944.527	Shape	0.257580307
			Scale	2.618394458

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

Table 25: Model parameters and goodness-of-fit criteria for Enco with cetuximab from BEACON CRC: PFS

Model	AIC	BIC	Parameter	Parameter value
Exponential	960.869	964.263	Intercept	-1.870866318
Generalised gamma	924.378	934.559	Mu	1.618183178
			Sigma	-0.205651431
			Q	0.248964411
Gompertz	956.835	963.622	Shape	0.049257034
			Rate	-2.07689693
Loglogistic	920.466	927.253	Shape	0.733311209
			Scale	1.529747453
Lognormal	924.196	930.984	Meanlog	1.525860038
			Sdlog	-0.165413959
Weibull	936.560	943.347	Shape	0.332153271
			Scale	1.888867243

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

To allow probabilistic modelling of the OS and PFS curves, Cholesky decompositions were generated from the variance-covariance matrices for each of the parametric models. The Cholesky decompositions are shown in Table 26 and Table 27 for OS and PFS, respectively.

Table 26: Cholesky decompositions for Enco with cetuximab, OS

Model	Parameter 1	Parameter 2	Parameter 3
Exponential (Parameter 1 = intercept)	0.08838834		
	0.109778417	-0.039710984	0.168705259
		0.094424622	-0.116421735

Generalised gamma (Parameter 1 = mu, Parameter 2 = sigma, Parameter 3 = q)			0.117349058
Gompertz (Parameter 1 = shape, Parameter 2 = rate)	0.017466019	-0.113689453	
		0.088380536	
Loglogistic (Parameter 1 = shape, Parameter 2 = scale)	0.074970791	-0.01714239	
		0.073099199	
Lognormal (Parameter 1 = meanlog, Parameter 2 = sdlog)	0.083003401	0.021664574	
		0.063141069	
Weibull (Parameter 1 = shape, Parameter 2 = scale)	0.073525519	-0.014896993	
		0.068317073	

Abbreviations: OS, overall survival.

Table 27: Cholesky decompositions for Enco with cetuximab, PFS

Model	Parameter 1	Parameter 2	Parameter 3
Exponential (Parameter 1 = intercept)	0.077382317		
Generalised gamma (Parameter 1 = mu, Parameter 2 = sigma, Parameter 3 = q)	0.090844019	-0.020345333	0.142143477
		0.060909757	-0.044359402
			0.113720855
Gompertz (Parameter 1 = shape, Parameter 2 = rate)	0.019056886	-0.086722941	
		0.077379608	
Loglogistic (Parameter 1 = shape, Parameter 2 = scale)	0.063694041	-0.004005124	
		0.059020574	
Lognormal (Parameter 1 = meanlog, Parameter 2 = sdlog)	0.061065197	0.00707546	
		0.055437373	
Weibull (Parameter 1 = shape, Parameter 2 = scale)	0.059317504	0.007112857	
		0.055512318	

Abbreviations: PFS, progression-free survival.

B.3.3.1.3 FOLFIRI: ITC (base-case)/BEACON CRC control (scenario)

B.3.3.1.3.1 ITC parameters

The base-case analysis for FOLFIRI used the outputs of an ITC to adjust the OS and PFS curves for Enco with cetuximab to generate curves for FOLFIRI. Full details of the ITC are described in Section B.2.10. The HRs used and their associated CIs, are shown in Table 28.

Table 28: HRs from ITC applied to Enco with cetuximab parametric model

OS HR (95% CI)	PFS HR (95% CI)
2.56 (1.23, 5.26)	3.33 (1.47, 7.14)

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

The method implemented in the model did not apply the HRs from the ITC to the model parameters used to specify the loglogistic models; rather, the HRs are applied directly to the curves generated from the parameters.

For the PSA, the HRs were sampled using the lognormal distribution.

B.3.3.1.3.2 Parametric model parameters

Whilst the ITC was selected as the base-case analysis, the economic model also allows for the data from the control arm of BEACON CRC to be used directly as a conservative proxy for FOLFIRI efficacy and is explored in a scenario analysis. As previously described in Section B.2.14.2.2.4, the efficacy data for FOLFIRI was derived from the control arm of the BEACON CRC trial, which comprised patients who were on one of the two following treatments:

- FOLFIRI with cetuximab.
- Irinotecan with cetuximab.

Following confirmatory consultation with clinical experts, it was determined that it was appropriate to assume the same efficacy for both FOLFIRI and irinotecan, and that data from the control arm could be used to inform the parametric models for FOLFIRI.

The presence of cetuximab means that the control arm is not directly applicable to inform estimates of relative effectiveness between Enco with cetuximab and FOLFIRI alone, as it is unclear how much benefit cetuximab provides to the overall regimen, based on limited empirical evidence within the BRAF-mutant subgroup. However expert clinical opinion suggests any benefit of cetuximab would be limited. As shown in Table 18 median OS estimates with FOLFIRI alone in small BRAF-mutant subgroups range between 4.2 and 5.7 months, whereas the control arm of BEACON CRC, (where cetuximab is used), provides a longer median OS of 5.88 months. In this context, although the BEACON CRC study may provide a robust evidence source, the inclusion of cetuximab in the control arm may lead to a modest overestimation of the effect of FOLFIRI when taken without cetuximab and therefore underestimate the additional benefit seen with the encorafenib regimen.

It should also be considered that in this scenario cetuximab is not costed for in the FOLFIRI arm of the economic model. The implications of this costing approach are discussed in further detail in Section B.3.5.1.1.2.

The parameters for each parametric model and their corresponding goodness-of-fit criteria (AIC and BIC) for OS and PFS are shown in Table 29 and Table 30 respectively.

Table 29: Model parameters and goodness-of-fit criteria for FOLFIRI based on BEACON CRC control arm: OS

Model	AIC	BIC	Parameter	Parameter value
Exponential	1009.823	1013.222	Intercept	-2.209628962
Generalised gamma	1003.563	1013.758	Mu	2.060138656
			Sigma	-0.070068662
			Q	0.622553616
Gompertz	1010.320	1017.117	Shape	0.022502794
			Rate	-2.326729156
Loglogistic	1000.316	1007.112	Shape	0.4951599
			Scale	1.818366567
Lognormal	1012.299	1019.095	Meanlog	1.804125254
			Sdlog	0.115629776
Weibull	1004.630	1011.426	Shape	0.181843456
			Scale	2.203633846

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

Table 30: Model parameters and goodness-of-fit criteria for FOLFIRI based on BEACON CRC control arm: PFS

Model	AIC	BIC	Parameter	Parameter value
Exponential	642.595	645.993	Intercept	-1.178894583
Generalised gamma	604.080	614.274	Mu	0.735877852
			Sigma	-0.084943608
			Q	-0.04826717
Gompertz	640.182	646.978	Shape	-0.067731004
			Rate	-1.01937832
Loglogistic	588.566	595.362	Shape	0.713933927
			Scale	0.691419998
Lognormal	602.198	608.994	Meanlog	0.755998585
			Sdlog	-0.089003043
Weibull	641.084	647.881	Shape	0.114232823
			Scale	1.196781404

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

The Cholesky decompositions for the above parametric models are shown in Table 31 and Table 32.

Table 31: Cholesky decompositions for FOLFIRI, OS

Model	Parameter 1	Parameter 2	Parameter 3
Exponential (Parameter 1 = intercept)	0.079808682		
Generalised gamma (Parameter 1 = mu, Parameter 2 = sigma, Parameter 3 = q)	0.105870145	-0.040999207	0.149448293
		0.075578782	-0.074819981
			0.111744981
Gompertz (Parameter 1 = shape, Parameter 2 = rate)	0.018034022	-0.097698679	
		0.079807741	
Loglogistic (Parameter 1 = shape, Parameter 2 = scale)	0.067147463	-0.006935487	
		0.073472695	
Lognormal (Parameter 1 = meanlog, Parameter 2 = sdlog)	0.081438673	0.010618063	
		0.057680471	
Weibull (Parameter 1 = shape, Parameter 2 = scale)	0.06492895	0.000436281	
		0.066539038	

Abbreviations: OS, overall survival.

Table 32: Cholesky decompositions for FOLFIRI, PFS

Model	Parameter 1	Parameter 2	Parameter 3
Exponential (Parameter 1 = intercept)	0.082478603		
Generalised gamma (Parameter 1 = mu, Parameter 2 = sigma, Parameter 3 = q)	0.091418848	-0.002202877	0.088549368
		0.060815203	-0.026656336
			0.104488473
Gompertz (Parameter 1 = shape, Parameter 2 = rate)	0.034238375	-0.07316356	
		0.08248603	
Loglogistic (Parameter 1 = shape, Parameter 2 = scale)	0.069454816	-0.009579471	
		0.063437514	
Lognormal (Parameter 1 = meanlog, Parameter 2 = sdlog)	0.070420998	0.007095914	
		0.059157832	
Weibull (Parameter 1 = shape, Parameter 2 = scale)	0.058930526	0.011465625	
		0.073575056	

Abbreviations: PFS, progression-free survival.

B.3.3.1.4 Trifluridine-tipiracil; naïve comparison

B.3.3.1.4.1 Digitisation and estimation of trifluridine-tipiracil IPD

The absence of comparative efficacy data meant that inclusion of trifluridine-tipiracil in the economic model was limited to a naïve comparison. As described in Section B.2.10.5 no studies were identified which assessed the efficacy of trifluridine-tipiracil in BRAF V600E-mutant mCRC patients. There were three studies which evaluated the efficacy of trifluridine-tipiracil in cohorts of patients for whom BRAF mutation status was not determined and who were assumed to be primarily BRAF wild-type (65-67). The largest of these trials was a global double-blind Phase 3 trial comprised of 800 mCRC patients randomised in a 2:1 ratio to either trifluridine-tipiracil or placebo (RECOURSE) (66). The trial presented K-M survival curves for OS and PFS alongside the number of patients at risk, which allowed an estimate of the IPD to be constructed using the methods described in Guyot 2012 (89). Baseline demographics for the RECOURSE trial are presented in Table 33. With the notable exclusion of BRAF V600E-mutant status, the baseline demographics are broadly similar to those of the BEACON CRC study.

Table 33: Key baseline characteristics of patients in the RECOURSE trial

Characteristic	Parameter	Trifluridine-tipiracil (n=534)	Placebo (n=266)
Age, years	Median	63	63
	Range	27-82	27-82
Sex, n (%)	Male	326 (61)	165 (62)
	Female	208 (39)	101 (38)
Race, n (%)	White	306 (57)	155 (58)
	Asian	184 (34)	94 (35)
	Black	4 (<1)	5 (2)
Region, n (%)	Japan	178 (33)	88 (330
	USA, Europe and Australia	356 (67)	178 (67)
ECOG performance status, n (%)	0	301 (56)	147 (55)
	1	233 (44)	119 (45)
Primary site of disease, n (%)	Colon	338 (63)	161 (61)
	Rectum	196 (37)	105 (39)
KRAS mutation, n (%)	No	262 (49)	131 (49)
	Yes	272 (51)	135 (51)
Time from diagnosis of metastases, n (%)	<18 months	111 (21)	55 (21)
	≥18 months	423 (79)	211 (79)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; KRAS, KRAS proto-oncogene, GTPase.
Source: Mayer 2015 (66).

The Guyot method of IPD estimation was chosen as it is currently the most sophisticated method available for estimating IPD from summary statistics and is recommended in NICE DSU TSD 14 (90).

B.3.3.1.4.2 Parametric model parameters

Parametric models were fitted to the reconstructed IPD. The parameters for the parametric models are shown in Table 34 and Table 35. The corresponding Cholesky decompositions are shown in Table 36 and Table 37.

Table 34: Model parameters and goodness-of-fit criteria for trifluridine-tipiracil from Mayer 2015: OS

Model	AIC	BIC	Parameter	Parameter value
Exponential	2438.367	2442.647	Intercept	-2.337489
Generalised gamma	2360.107	2372.948	Mu	2.1347
			Sigma	-0.2447462
			Q	0.4987
Gompertz	2408.460	2417.020	Shape	0.07190979
			Rate	-2.71570663
Loglogistic	2353.473	2362.034	Shape	0.6985416
			Scale	1.9755423
Lognormal	2371.367	2379.928	Meanlog	1.972464
			Sdlog	-0.105826
Weibull	2369.837	2378.398	Shape	0.3931132
			Scale	2.2869285

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

Table 35: Model parameters and goodness-of-fit criteria for trifluridine-tipiracil from Mayer 2015: PFS

Model	AIC	BIC	Parameter	Parameter value
Exponential	2208.645	2212.925	Intercept	-1.228934
Generalised gamma	2001.787	2014.628	Mu	0.7723394
			Sigma	-0.3303078
			Q	-0.4382495
Gompertz	2206.156	2214.717	Shape	0.03546067
			Rate	-1.3259943
Loglogistic	2015.747	2024.308	Shape	0.8629167
			Scale	0.877762
Lognormal	2016.782	2025.342	Meanlog	0.9272101
			Sdlog	-0.3027391
Weibull	2147.006	2155.567	Shape	0.2852553
			Scale	1.2955694

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

Table 36: Cholesky decompositions for trifluridine-tipiracil, OS

Model	Parameter 1	Parameter 2	Parameter 3
Exponential (Parameter 1 = intercept)	0.05234239		
Generalised gamma (Parameter 1 = mu, Parameter 2 = sigma, Parameter 3 = q)	0.05777349	-0.02578131	0.10344203
		0.05067102	-0.05486446
			0.07305134
Gompertz (Parameter 1 = shape, Parameter 2 = rate)	0.01217323	-0.07142223	
		0.05234242	
Loglogistic (Parameter 1 = shape, Parameter 2 = scale)	0.04409224	-0.005196578	
		0.038420489	
Lognormal (Parameter 1 = meanlog, Parameter 2 = sdlog)	0.04220364	0.008756144	
		0.037807421	
Weibull (Parameter 1 = shape, Parameter 2 = scale)	0.04257929	-0.00194596	
		0.03532861	

Abbreviations: OS, overall survival.

Table 37: Cholesky decompositions for trifluridine-tipiracil, PFS

Model	Parameter 1	Parameter 2	Parameter 3
Exponential (Parameter 1 = intercept)	0.04494665		
Generalised gamma (Parameter 1 = mu, Parameter 2 = sigma, Parameter 3 = q)	0.04740051	0.007605796	0.075403608
		0.031996687	-0.001537689
			0.067600796
Gompertz (Parameter 1 = shape, Parameter 2 = rate)	0.01631757	-0.04674939	
		0.04494666	
Loglogistic (Parameter 1 = shape, Parameter 2 = scale)	0.03730258	-0.002948448	
		0.031835574	
Lognormal (Parameter 1 = meanlog, Parameter 2 = sdlog)	0.03222865	0.001228668	
		0.032270657	
Weibull (Parameter 1 = shape, Parameter 2 = scale)	0.03293865	0.009363636	
		0.033791895	

Abbreviations: PFS, progression-free survival.

B.3.3.1.4.3 Implementation of BRAF V600E versus BRAF wild-type HR

As the RECOURSE trial was conducted in a population which was assumed to be primarily BRAF wild-type (BRAF mutation status was not explicitly reported in the publication), a HR was applied to the fitted parametric models for OS and PFS to adjust for the fact that BRAF V600E mCRC patients have significantly worse OS and PFS outcomes than BRAF wild-type patients (e.g. median OS 4.2 months in BRAF-mutant mCRC vs 15.5 months in RAS/BRAF wild-type when both treated with FOLFIRI at second-line (28)).

An analysis conducted by Peeters 2015 investigated the OS and PFS outcomes associated with the BRAF V600E mutation versus BRAF wild-type (42); the HRs for the relationship between BRAF-mutant and wild-type on OS and PFS outcomes are presented in Table 38. The reciprocals of the presented HRs and their CIs were used in the model (i.e. 4.00 for OS and 3.56 for PFS) due to the reference population being BRAF V600E-mutant rather than BRAF wild-type as in the Peeters trial. The impact of implementing the HRs on the OS and PFS curves from the RECOURSE study (Mayer 2015) is presented in Figure 14 and Figure 15.

Due to the magnitude of the adjustment HRs, two alternative scenarios were also investigated where the efficacy of trifluridine-tipiracil was assumed to be more optimistic. One extreme scenario assumed equivalence with FOLFIRI as per the ITC although clinical experts have advised that trifluridine-tipiracil patients would be expected to have worse

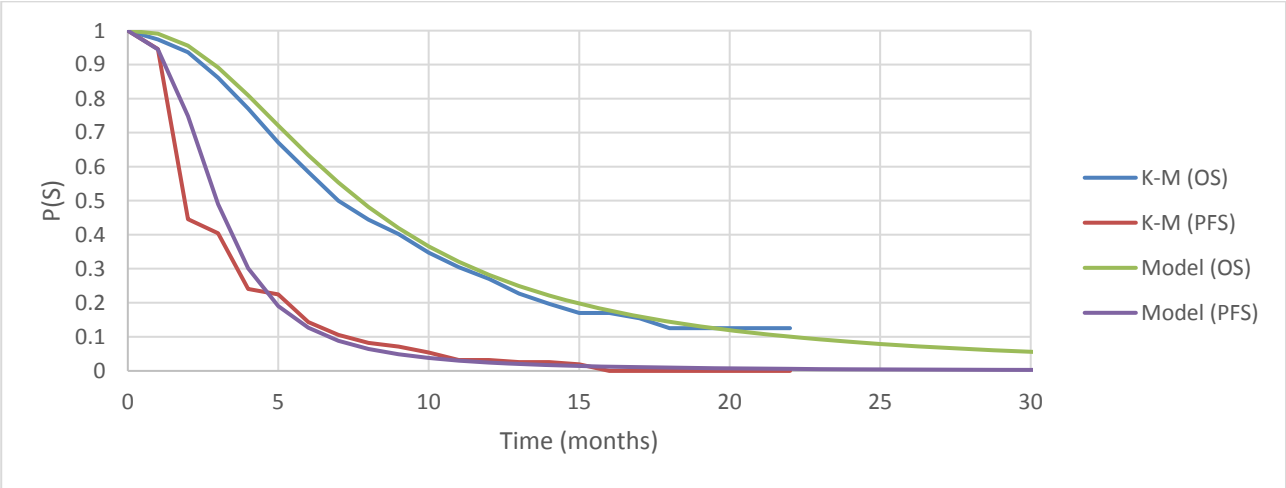
outcomes than FOLFIRI patients. A second scenario used alternative adjustment HRs from a meta-analysis by Safaee Ardekani (27); this study only provided HRs for OS and not for PFS, hence was not used in the base-case analysis. Scenarios are presented in Section B.3.8.4.

Table 38: BRAF V600E adjustment HRs

Outcome	HR (95% CI), BRAF wild-type versus BRAF V600E	HR (95% CI), BRAF V600E versus BRAF wild-type (used in model)
OS	0.25 (0.18, 0.36)	4.00 (2.78, 5.56)
PFS	0.28 (0.20, 0.40)	3.57 (2.50, 5.00)

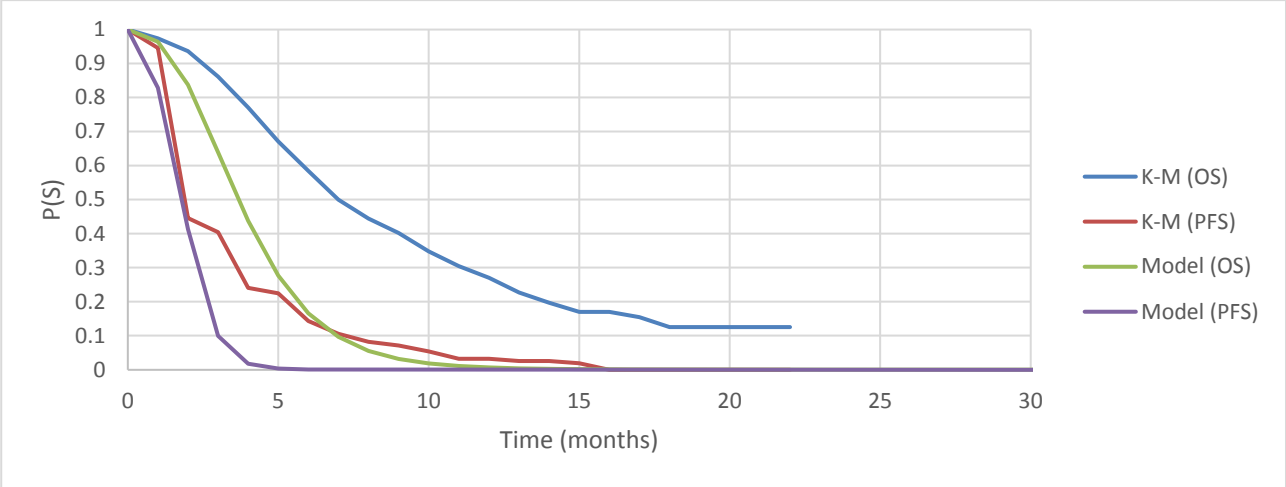
Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
Source: Peeters 2015 (42).

Figure 14: Trifluridine-tipiracil OS and PFS curves without BRAF V600E adjustment applied



Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

Figure 15: Trifluridine-tipiracil OS and PFS curves with BRAF V600E adjustment applied



Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

B.3.3.1.5 Time to discontinuation

Time to discontinuation (TTD) was assumed to be equivalent to PFS, i.e. if a patient was in the pre-progression health state, they would be on treatment, and if a patient was in the post-progression health state, they would be off treatment. This approach was corroborated by feedback from clinical experts who stated that the assumption that PFS is equal to TTD is reflective of current clinical practice. This assumption was further validated by an exploratory analysis which did not find a statistically significant difference between the PFS curves and the TTD curves based on the duration of treatment exposure parameter in the IPD (Enco with cetuximab p=0.46, control p=0.19; log-rank test; Figure 16 and Figure 17, respectively).

Figure 16: TTD and PFS K-M curves for the Enco with cetuximab arm

Abbreviations: K-M, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation.

Figure 17: TTD and PFS K-M curves for the BEACON CRC control arm

Abbreviations: K-M, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.3.3.2 Adverse events

AEs are applied in the model as one-off costs and do not belong to any health state; the costs of treating individual AEs are described in detail in Section B.3.5.3. HRQoL decrements due to AEs are included within utility values estimated from BEACON CRC patients (Section B.3.4.5) and therefore no additional AE disutilities are included in the model to avoid double-counting.

The economic model incorporates AEs likely to have a notable impact on costs, namely those of severity Grade 3+ with an incidence of at least 2% in either the Enco with cetuximab arm of BEACON CRC, the FOLFIRI arm of RAISE (91) or the trifluridine-tipiracil arm of the RECOURSE trial (66).

The AE rates from BEACON CRC are described in detail in Section B.2.11.1.

As patients in the control arm of BEACON CRC were on FOLFIRI or irinotecan in combination with cetuximab, some AEs may have been attributable to cetuximab, and thus the control arm may not be a fair reflection of the AE profile expected with FOLFIRI alone. To address this, AE rates were sourced from a large Phase 3 RCT which compared ramucirumab with FOLFIRI versus FOLFIRI alone in patients with mCRC (RAISE). This RCT was identified in the RCT SLR (see Appendix D, Section D.1.1, Table 4) as a source of BRAF-mutant efficacy data and was considered for its inclusion in NMA (28); however no AE data specifically in the BRAF-mutant population were reported in this publication. Consequently, the primary publication for the RAISE study was used to identify AE rates across the entire trial cohort (Tabernero 2015 (91)). The patient population in RAISE predominantly included patients who were BRAF wild-type; 41 of the 1,072 patients enrolled possessed the BRAF V600E mutation (91).

The FOLFIRI study included in the grouped nodes ITC (Study 20050181/NCT0039183; ITC described in Section B.2.10) was not used as the source of Grade 3+ AEs because AEs were not reported in a suitable format in any of the study publications identified by the SLR (42, 92, 93).

The AEs included in the model are shown in Table 39 for clarity.

Table 39: Grade 3+ AEs from Enco with cetuximab arm of BEACON CRC, FOLFIRI arm of RAISE and trifluridine-tipiracil arm of RECOURSE (AEs ≥2%)

AE	Enco with cetuximab†	FOLFIRI‡	Trifluridine/ tipiracil§
Abdominal pain	3.2%	3.6%	2.4%
Anaemia	[redacted]	3.6%	18.2%
Asthenia	3.7%	0.0%	3.4%
Cancer pain	2.3%	0.0%	0.0%
Decreased appetite	[redacted]	1.9%	3.6%
Diarrhoea	2.8%	9.7%	3.0%
Fatigue	4.2%	7.8%	3.9%
Febrile neutropenia	[redacted]	2.5%	3.8%
Hypertension	[redacted]	2.8%	0.0%
Intestinal obstruction	4.6%	0.0%	0.0%
Leukopenia	[redacted]	2.7%	21.4%
Liver injury/ failure	[redacted]	4.0%	0.0%
Nausea	0.0%	2.7%	0.0%

AE	Enco with cetuximab†	FOLFIRI‡	Trifluridine/ tipiracil§
Neutropenia	[redacted]	23.3%	37.9%
Stomatitis	[redacted]	2.3%	0.0%
Thrombocytopenia	[redacted]	0.8%	5.1%
Urinary tract infection	2.3%	0.0%	0.0%
Venous thrombosis	[redacted]	2.1%	0.0%
Vomiting	1.4%	2.5%	2.1%

Abbreviations: AE, adverse event.
† AE rates from Enco with cetuximab arm of BEACON CRC; ‡ AE rates from placebo (FOLFIRI) arm of RAISE (91); § AE rates from trifluridine/tipiracil arm of RECOURSE (66).

The incidence of each AE was used as a weight for the AE costs detailed in Section B.3.5.3. The impact of AEs was considered for the first model cycle only.

The number of patients experiencing each AEs and the total number of patients in the respective treatment arm were used to parameterise beta distributions which were used in the PSA.

B.3.3.3 Expert involvement

Two research activities were conducted to elicit information and test assumptions for the economic model, involving NHS consultant oncologists and external health economists.

The final model structure, key assumptions and inputs were validated during an advisory board in December 2019 by two clinical (consultant oncologists) and three health economic experts in the UK with significant NHS experience in the treatment of mCRC and with experience of oncology health economic modelling, respectively. All experts were provided with information on the model concept and proposed inputs and extrapolations.

Input from a third clinical expert (consultant oncologist) was also sought via a face to face meeting and follow up teleconference, with the main objective being to ensure the clinical plausibility of the model structure and assumptions.

Specific assumptions were checked as necessary with follow-up emails and phone calls to both the clinical and health economic experts.

One of the clinical experts and two of the health economists have also participated in a global advisory board to support the collation of inputs. No further direct financial or non-financial conflicts are applicable.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from BEACON CRC

The EQ-5D-5L was used to measure the HRQoL of patients in the BEACON CRC trial. To adhere to the NICE reference case, EQ-5D-3L-based utilities were generated based on the gathered EQ-5D-5L data for the August 2019 data cut. The EQ-5D-3L utility values were generated using the cross walking method developed by van Hout 2012 (94), as per the NICE reference case and NICE's current position on the use of the EQ-5D-5L value set (78, 95).

Health states were defined by progression status and were determined separately for each treatment arm of BEACON CRC; as for the OS and PFS assumptions, the BEACON CRC control arm was used to determine HRQoL for the purposes of modelling FOLFIRI.

The utility values were split into the following categories based on the time points the utility values were captured at. The split was defined as the following:

- Pre-progression: Baseline, Cycle 1 … Cycle n.
- Post-progression: End of treatment, 30-day follow-up.

This method assumed that PFS and TTD are coupled, i.e. that if a patient was currently receiving treatment, then they had not progressed, and vice versa. The EQ-5D-3L utility values derived using this method are shown in Table 40.

Table 40: Utility values generated (BEACON CRC August 2019 dataset)

	Enco with cetuximab		BEACON CRC control arm	
	Pre-progression	**Post-progression**	**Pre-progression**	**Post-progression**
Mean	0.743	0.622	0.741	0.631
SD	0.195	0.252	0.193	0.279
n	1,344	147	591	161
SE	0.005319	0.020785	0.007939	0.021988

Abbreviations: SD, standard deviation; SE, standard error.

No imputation of missing data were performed due to the low frequency of incomplete EQ-5D-5L results; analysis was performed on complete cases only. The number of complete records that were available for each analysis are shown in Table 41. Please note that the screening visit was excluded from the calculation of pre-progression utility.

Table 41: Number of EQ-5D-5L completed questionnaires at each time point by treatment and health state (BEACON CRC August 2019 dataset)

Visits	Enco with cetuximab			BEACON CRC control arm		
	Completed	Not completed	Not completed (%)	Completed	Not completed	Not completed (%)
All visits	1,491	13	0.87%	752	4	0.53%

Abbreviations: EQ-5D, EuroQoL-5 dimensions-5 levels.

B.3.4.2 Mapping

As described in Section B.3.4.1, the domain-level EQ-5D-5L scores were cross walked to the EQ-5D-3L using the UK tariff following the methods developed by van Hout 2012 (94). The IPD domain-level scores were recorded from BEACON CRC and the "eq5d" package in R was used to generate EQ-5D-3L utility values for pre-progression and post-progression health states using the UK value set. No additional mapping was required or performed.

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

An SLR was conducted to identify utility data for potential use in the model; the search was limited to sourcing utility data for active treatments in the NICE scope comparator list and company decision problem (FOLFIRI or trifluridine-tipiracil) when administered at second- and later lines of therapy, unless the study was specifically in BRAF-mutant mCRC, in which case no intervention restriction was applied (see Appendix H).

The search did not identify any utility values which were specific to BRAF-mutant mCRC populations. Ten studies (two full publications and eight conference abstracts) reported health state utility values (HSUVs) for patients with mCRC (BRAF status not specified) treated with either FOLFIRI or trifluridine-tipiracil when given at second- or third-line (see Appendix H, Table 17).

B.3.4.4 Adverse events

The utility values used in the model have been derived directly from data collected as part of the BEACON CRC trial and as such they consider the negative impacts on HRQoL associated with any treatment-related AEs. No further separate one-off disutility for AEs was included in the model, although the model has the capacity to include disutilities in scenario analyses if required.

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

B.3.4.5.1 Utilities used

The EQ-5D analyses from the BEACON CRC data described in Section B.3.4.1 were used to estimate utility for all interventions in the model; for Enco with cetuximab data was taken specifically from the Enco with cetuximab arm and for FOLFIRI from the BEACON CRC control arm. To estimate the utility of patients on trifluridine-tipiracil, the mean of the Enco with cetuximab and control arm utilities was taken for each health state.

By using EQ-5D-5L data gathered in the BEACON CRC trial directly, the model uses the highest-quality form of HRQoL data available as it is directly representative of the study population with BRAF-mutant mCRC.

All utility values used in the base-case economic model are sourced from BEACON CRC.

No studies were identified in the SLR which provided HSUVs in a BRAF-mutant population; given that trifluridine-tipiracil was not part of the BEACON CRC trial relevant utility values derived from non-BRAF-mutant studies were considered in scenario analysis (see Section B.3.8.4).

B.3.4.5.2 Key drivers of utility

Clinical expert feedback indicated that the primary driver of HRQoL in mCRC patients is their progression status and not the treatment they are on. However, as the granularity of the QoL data captured in the trial allowed for the calculation of utilities based on treatment arm as well as progression status, utilities were captured separately for each treatment arm. Utility values were similar across treatments arms in both the pre-progression and post-progression health states (Section B.3.4.1).

B.3.4.5.3 Age-related utility decrements

As the patient population in BEACON CRC had a mean age of 59.3 years, age-related utility decrements were considered as per the methods described in Ara and Brazier 2010 (96). The linear regression model described below was used to determine the mean utility of the general population:

$$EQ5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

The general population utility for the population as it entered the model (0.829 given an age of 59.3 years and 47.2% of the cohort being male) was used to determine a utility

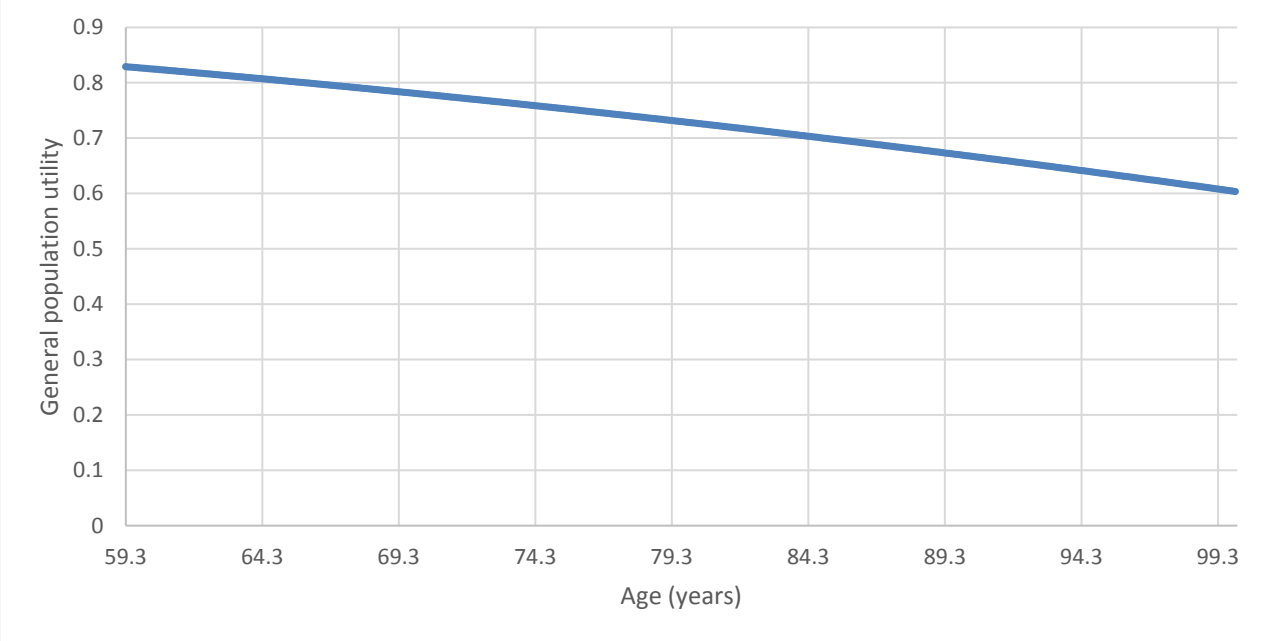
multiplier which was to be applied to the utility values for the pre-progression and post-progression health states. The calculated multipliers are shown in Table 42.

Table 42: Implementation of Ara and Brazier general population utility algorithm using Enco with cetuximab utility values

Data	Pre-progression	Post-progression
Utility from trial	0.743	0.622
General population utility on model entry	0.829	0.829
Calculated utility multiplier	0.896	0.751

The multipliers were then applied to the general population utility, which was calculated for each cycle to generate correct age-related utility values for the pre-progression and post-progression health states across all treatments. The derived general population utility is shown in Figure 18.

Figure 18: General population utility over time as per the Ara and Brazier† general population utility algorithm



† Ara and Brazier 2010 (96).
59.3 years represents the mean age of patients as they entered the BEACON CRC trial.

A summary of the utility values used in the base-case are presented in Table 43.

Table 43: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission (section and page number)	Justification
Enco with cetuximab: pre-progression	0.743 (0.005)	0.732, 0.753	Section B.3.4.1, page 124	Trial-derived utility values using latest data set available; highest-quality data available.
Enco with cetuximab: post-progression	0.622 (0.021)	0.582, 0.663	0, page 124	
FOLFIRI: pre-progression	0.741 (0.008)	0.725, 0.756	0, page 124	
FOLFIRI: post-progression	0.631 (0.022)	0.558, 0.661	0, page 124	
Trifluridine-tipiracil: pre-progression	0.742 (N/A)	N/A	0, page 124	Mean of Enco with cetuximab and FOLFIRI utilities; lack of trifluridine-tipiracil-specific utility values in the SLR
Trifluridine-tipiracil: post-progression	0.627 (N/A)	N/A	0, page 124	

Abbreviations: CI, confidence interval; N/A, not applicable; SE, standard error; SLR, systematic literature review.
Note that the utility values reported are subsequently adjusted for age.

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

The current analysis was developed with the aim of including costs that would closely represent the actual costs of treatment for the NHS and Personal Social Services in England.

The following costs are included in the model:

- Cost of primary treatment (intervention and comparators in the model), including drug costs, dispensing and administration costs.
- Cost of subsequent treatments including drug costs, dispensing and administration costs.
- Resource use costs.
- Cost of treating AEs.
- Terminal care at the end of life.

Primary treatment costs are applied to the patients for as long as they are on treatment, as determined by the PFS curve. In the base-case, all patients are assumed to receive subsequent treatment upon discontinuation from primary treatment and this is applied as a one-off cost at the time of discontinuation; subsequent treatment costs are described in further detail in Section B.3.5.1.2.

Resource use costs are applied based on health state (pre-progression or post-progression). These are independent of all other costs and are described in Section B.3.5.2.

The costs of treating AEs are assumed to only apply in the first cycle of the model; these are described in Section B.3.5.3.

The terminal care costs are applied as a one-off cost at the point of death; terminal costs are described in Section B.3.5.4.

Drug costs were sourced from the drugs and pharmaceutical electronic market information tool (eMIT) provided by the Department of Health and Social Care (97) if available and unless specified otherwise; other sources included BNF (10), NICE TA405 documentation (31) or confidential sources (Pierre Fabre patient access scheme [PAS] price). The eMIT data provides the average price paid for each drug in the database over the last 4 months of the period; the latest version of the eMIT represents the 12-month period to the end of June 2019. The standard deviation of the drug price was also available from the eMIT database; this was used to parameterise gamma distributions for the drug prices in the PSA.

It was assumed that vial sharing would occur where possible, as opposed to vial wastage where the remainder of an IV-administered drug would be discarded after use. This assumption was made following input from clinical experts, who stated that in clinical practice effort would be made to share vials between patients in order to minimise costs.

A specific cost and resource use SLR was not conducted. UK-based cost-effectiveness studies identified in the cost-effectiveness SLR (Appendix G) were assessed to identify any cost and resource use data for possible inclusion in the model. Specific cost sources and justifications for each are provided in the subsequent subsections.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Primary treatments

B.3.5.1.1.1 Intervention costs

The dose of Enco was implemented in the model in line with the dosing recommendation in the anticipated marketing authorisation and as used in the BEACON CRC study. For cetuximab, dosing was in line with NHSE CDF guidance (and as used in clinical practice) and differs from SmPC recommendations on the frequency of dosing (see below).

Cetuximab was dosed according to BSA, therefore National Dose Banding tables were used to calculate the dose (98). The BSA was assumed to be the mean BSA from BEACON CRC; 1.79m^2, as presented in Table 21.

Encorafenib was priced based on the PAS price approved by the Department of Health. The cost of cetuximab was assumed to be the list price as per BNF (10), as the commercial access arrangement for cetuximab is not in the public domain.

RDI multipliers were used to account for the proportion of patients who remained on primary treatment but with a dose reduction based on data from BEACON CRC. RDI is an estimate of the ratio between the actual cumulative dose (in mg) and the planned cumulative doses. The total dose per drug cycle of 28 days was calculated by multiplying the total daily dose (corrected for mean RDI) by the number of days in the drug cycle and then rounding up to the nearest whole tablet (or vial for IV drugs). The RDIs used in the model are presented in Section B.2.11.1.1.

Table 44. Cost components of the Enco with cetuximab treatment regimen

	mg per tablet/ vial	Tablets/ vials per pack	List price per pack	PAS discount	PAS price per pack	mg/m^2	Dose per admin	Mean RDI (E+C)	Frequency per drug cycle	Length of drug cycle
Encorafenib	75	42	£1,400.00	[redacted]	[redacted]	-	300	[redacted]	28	28
Cetuximab (initiation)	500	1	£890.50	0.00%	£890.50	400	700	[redacted]	1	7
Cetuximab (maintenance)	500	1	£890.50	0.00%	£890.50	500	900	[redacted]	1	14

Abbreviations: E+C, encorafenib with cetuximab; PAS, patient access scheme; RDI, relative dose intensity.

Encorafenib

The recommended dose is 300 mg (four 75 mg capsules) QD when used in combination with cetuximab.

Cetuximab

Prior to the first infusion patients must receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions (4). The premedication costs for Enco with cetuximab are listed in Table 45. No RDI assumptions were made for premedication drugs, such that the RDI used is effectively 1.

Table 45: Premedication costs for Enco with cetuximab

	mg per tablet / vial	Tablets / vials per pack	List price/ pack	Cost/ tablet or vial	Cost/ mg	Dose/ admi n	Vials/ tablets per admin	Freq./ drug cycle	Length of drug cycle	Cost/ model cycle
Chlorphenamine	10	5	£12.14	£2.43	£0.243	10	1.00	1	7	£10.55
Hydrocortisone	100	10	£9.09	£0.91	£0.009	100	1.00	1	7	£3.95
Paracetamol	500	16	£0.11	£0.01	£0.000	1000	2.00	1	7	£0.06

The SmPC recommendation on cetuximab dosing is an initial dose of 400 mg per m^2 body surface area, followed by 250 mg/m^2 for all subsequent doses given once weekly (4).

In contrast, CDF guidance from NHS England, which guides clinical practice in England, recommends a maintenance dosing schedule of 500 mg/m^2 given every 2 weeks (5). This assumption is used in the base-case as it is reflective of current NHS clinical practice and as accepted previously in NICE TA439.

The total monthly costs for Enco with cetuximab are shown in Table 46.

Table 46: Primary treatment costs per model cycle for Enco with cetuximab†

Intervention	Drug cost per model cycle excluding RDI (£)		Drug cost per model cycle based on RDI¥ (£)		Total cost per model cycle including admin cost inc. RDI (£)	
	List	PAS	List	PAS	List	PAS
Encorafenib	£4,055.56	[redacted]	£4,055.56	[redacted]		
Cetuximab, initiation cycle‡	£1,246.70	£1,246.70	£1,083.51	£1,083.51		
Cetuximab, maintenance	£3,482.49	£3,482.49§	£3,026.64	£3,026.64§		
Enco with cetuximab, maintenance	£7,538.05	[redacted]§	£7,082.20	[redacted]§	£8,045	£[redacted]§

Abbreviations: PAS, patient access scheme; RDI, relative dose intensity.
†Model cycle = 30.42 days; ‡Cetuximab initiation costs shown here are for a one-week induction period; patients start treatment 1 week after this initiation, and incur 50% of the costs of a typical maintenance cycle as well. The additional maintenance costs are included here; §Cetuximab, marketed by Merck Serono is subject to a confidential commercial arrangement, which the NHSE have confirmed is applicable to combination treatment with Enco in the mCRC setting. Pierre Fabre are not party to the discount applicable. The PAS price does not include any assumed discount for cetuximab; ¥ Please note that at an RDI of 1, encorafenib patients require four tablets to meet their dose requirements. The RDI would need to be equal to or less than 0.75 for patients to require three tablets, and lead to a cost reduction.

B.3.5.1.1.2 Comparator costs

FOLFIRI and trifluridine-tipiracil are dosed according to BSA and therefore the mean BSA from BEACON CRC is assumed (see Section B.3.5.1.1.1). The folinic acid, fluorouracil and irinotecan SmPCs (68-70) and National Dose Banding tables are used to calculate the

doses for the components of FOLFIRI (99-102) and the dosing table in the SmPC is used for trifluridine-tipiracil (71). A summary of the data sources used for posology information is presented in Table 47.

Table 47: Dosing information data sources for FOLFIRI and trifluridine-tipiracil

Treatment	Dosing information data source
FOLFIRI	Folinic acid SmPC (68) Fluorouracil SmPC (69) Irinotecan SmPC (70)
Trifluridine-tipiracil	Trifluridine-tipiracil SmPC (71)

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; SmPC, summary of product characteristics.

The costs of the components of FOLFIRI (folinic acid/fluorouracil/irinotecan) are sourced from CMU eMIT (97) as this represents the average price paid by the NHS for each treatment. As a number of different medicinal forms (tablet/ vials per pack, concentration of treatments) were available, the treatment costs were calculated for each medicinal form then the average cost per cycle for each of the forms was taken. Variance data are also presented in the CMU eMIT costs; these data were used to vary costs probabilistically in the PSA.

The cost of trifluridine-tipiracil is based on list price provided in the BNF for the only formulation available (Lonsurf) with an inferred [redacted] PAS discount applied, as the PAS price per treatment cycle [redacted] was provided on page 2 of the FAD for TA405 (31).

The costs per pack for each of the comparators are listed in Table 48.

Table 48: Unit costs used for comparators

Regimen	Drug	Mg per tablet / vial	Tablets / vials per pack	Cost per pack
FOLFIRI	Calcium folinate 100mg/10ml solution for injection vials (Folinic acid)	100	1	£2.40
FOLFIRI	Calcium folinate 100mg/10ml solution for injection vials (Folinic acid)	100	10	£11.84
FOLFIRI	Calcium folinate 300mg/30ml solution for injection vials (Folinic acid)	300	1	£3.71
FOLFIRI	Calcium folinate 350mg/35ml solution for injection vials (Folinic acid)	350	1	£5.36
FOLFIRI	Calcium folinate 350mg/35ml solution for injection vials (Folinic acid)	350	10	£49.98
FOLFIRI	Calcium folinate 50mg/5ml solution for injection vials (Folinic acid)	50	1	£2.43

Regimen	Drug	Mg per tablet / vial	Tablets / vials per pack	Cost per pack
FOLFIRI	Calcium folinate 50mg/5ml solution for injection vials (Folinic acid)	50	10	£15.42
FOLFIRI	Fluorouracil 1g/20ml (5%) solution for infusion vials	1000	1	£1.13
FOLFIRI	Fluorouracil 2.5g/100ml (2.5%) solution for infusion vials	2500	1	£2.68
FOLFIRI	Fluorouracil 2.5g/50ml (5%) solution for infusion vials	2500	1	£2.27
FOLFIRI	Fluorouracil 250mg/10ml (2.5%) solution for infusion vials	250	5	£23.76
FOLFIRI	Fluorouracil 500mg/10ml (5%) solution for infusion vials	500	1	£0.98
FOLFIRI	Fluorouracil 500mg/20ml (2.5%) solution for infusion vials	500	10	£66.00
FOLFIRI	Fluorouracil 5g/100ml (5%) solution for infusion	5000	1	£3.19
FOLFIRI	Irinotecan 100mg/5ml solution for infusion	100	1	£4.60
FOLFIRI	Irinotecan 300mg/15ml solution for infusion vials	300	1	£11.36
FOLFIRI	Irinotecan 40mg/2ml solution for infusion vials	40	1	£3.14
FOLFIRI	Irinotecan 500mg/25ml solution for infusion vials	500	1	£16.73
Trifluridine-tipiracil	Trifluridine-tipiracil 20mg	20	60	[redacted]
Trifluridine-tipiracil	Trifluridine-tipiracil 15mg	15	60	[redacted]

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; mg, milligram; ml, millilitre.

From the cost per pack, the cost per tablet/vial for each drug was taken. This was then used to calculate a cost per milligram. The dose in milligrams per metre squared was then used in conjunction with National Dosing Tables to determine the total dose of each treatment received per administration. The dose per administration is shown in Table 49.

Table 49: Cost per mg and dose per administration used for comparators

Regimen	Drug	Cost per tablet/ vial	Cost per mg	Mg dose per m^2
FOLFIRI	Calcium folinate 100mg/10ml solution for injection vials (Folinic acid)	£2.40	£0.02	400
FOLFIRI	Calcium folinate 100mg/10ml solution for injection vials (Folinic acid)	£1.18	£0.01	400
FOLFIRI	Calcium folinate 300mg/30ml solution for injection vials (Folinic acid)	£3.71	£0.01	400

Regimen	Drug	Cost per tablet/ vial	Cost per mg	Mg dose per m^2
FOLFIRI	Calcium folinate 350mg/35ml solution for injection vials (Folinic acid)	£5.36	£0.02	400
FOLFIRI	Calcium folinate 350mg/35ml solution for injection vials (Folinic acid)	£5.00	£0.01	400
FOLFIRI	Calcium folinate 50mg/5ml solution for injection vials (Folinic acid)	£2.43	£0.05	400
FOLFIRI	Calcium folinate 50mg/5ml solution for injection vials (Folinic acid)	£1.54	£0.03	400
FOLFIRI	Fluorouracil 1g/20ml (5%) solution for infusion vials	£1.13	£0.00	2800
FOLFIRI	Fluorouracil 2.5g/100ml (2.5%) solution for infusion vials	£2.68	£0.00	2800
FOLFIRI	Fluorouracil 2.5g/50ml (5%) solution for infusion vials	£2.27	£0.00	2800
FOLFIRI	Fluorouracil 250mg/10ml (2.5%) solution for infusion vials	£4.75	£0.02	2800
FOLFIRI	Fluorouracil 500mg/10ml (5%) solution for infusion vials	£0.98	£0.00	2800
FOLFIRI	Fluorouracil 500mg/20ml (2.5%) solution for infusion vials	£6.60	£0.01	2800
FOLFIRI	Fluorouracil 5g/100ml (5%) solution for infusion	£3.19	£0.00	2800
FOLFIRI	Irinotecan 100mg/5ml solution for infusion	£4.60	£0.05	180
FOLFIRI	Irinotecan 300mg/15ml solution for infusion vials	£11.36	£0.04	180
FOLFIRI	Irinotecan 40mg/2ml solution for infusion vials	£3.14	£0.08	180
FOLFIRI	Irinotecan 500mg/25ml solution for infusion vials	£16.73	£0.03	180
Trifluridine-tipiracil	Trifluridine-tipiracil 20mg	[redacted]	[redacted]	35
Trifluridine-tipiracil	Trifluridine-tipiracil 15mg	[redacted]	[redacted]	35

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; mg, milligram; ml, millilitre.

The RDIs and calculated vials / tablets per administration along with the duration of the drug cycles are shown in Table 50.

Table 50: RDIs, vials / tablets per administration, and length of treatment cycles used for comparators

Regimen	Drug	RDI	Vials/ tablets per administration	Length of drug cycle (days)
FOLFIRI	Calcium folinate 100mg/10ml solution for injection vials (Folinic acid)	0.716	5.01	14
FOLFIRI	Calcium folinate 100mg/10ml solution for injection vials (Folinic acid)	0.716	5.01	14
FOLFIRI	Calcium folinate 300mg/30ml solution for injection vials (Folinic acid)	0.716	1.67	14
FOLFIRI	Calcium folinate 350mg/35ml solution for injection vials (Folinic acid)	0.716	1.43	14
FOLFIRI	Calcium folinate 350mg/35ml solution for injection vials (Folinic acid)	0.716	1.43	14
FOLFIRI	Calcium folinate 50mg/5ml solution for injection vials (Folinic acid)	0.716	10.02	14
FOLFIRI	Calcium folinate 50mg/5ml solution for injection vials (Folinic acid)	0.716	10.02	14
FOLFIRI	Fluorouracil 1g/20ml (5%) solution for infusion vials	0.673	3.36	14
FOLFIRI	Fluorouracil 2.5g/100ml (2.5%) solution for infusion vials	0.673	1.35	14
FOLFIRI	Fluorouracil 2.5g/50ml (5%) solution for infusion vials	0.673	1.35	14
FOLFIRI	Fluorouracil 250mg/10ml (2.5%) solution for infusion vials	0.673	13.46	14
FOLFIRI	Fluorouracil 500mg/10ml (5%) solution for infusion vials	0.673	6.73	14
FOLFIRI	Fluorouracil 500mg/20ml (2.5%) solution for infusion vials	0.673	6.73	14
FOLFIRI	Fluorouracil 5g/100ml (5%) solution for infusion	0.673	0.67	14
FOLFIRI	Irinotecan 100mg/5ml solution for infusion	0.725	2.32	14
FOLFIRI	Irinotecan 300mg/15ml solution for infusion vials	0.725	0.77	14
FOLFIRI	Irinotecan 40mg/2ml solution for infusion vials	0.725	5.80	14
FOLFIRI	Irinotecan 500mg/25ml solution for infusion vials	0.725	0.46	14
Trifluridine-tipiracil	Trifluridine-tipiracil 20mg	1.000	6.00	28
Trifluridine-tipiracil	Trifluridine-tipiracil 15mg	1.000	8.00	28

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; mg, milligram; ml, millilitre; RDI, relative dose intensity.

The calculated costs used for the comparators, taking into consideration Table 48, Table 49 and Table 50 are shown in Table 51.

Table 51: Cost per regimen per model cycle

Regimen	Drug	Total cost per model cycle†
FOLFIRI	Calcium folinate 100mg/10ml solution for injection vials (Folinic acid)	£26.12
FOLFIRI	Calcium folinate 100mg/10ml solution for injection vials (Folinic acid)	£12.89
FOLFIRI	Calcium folinate 300mg/30ml solution for injection vials (Folinic acid)	£13.46
FOLFIRI	Calcium folinate 350mg/35ml solution for injection vials (Folinic acid)	£16.67
FOLFIRI	Calcium folinate 350mg/35ml solution for injection vials (Folinic acid)	£15.54
FOLFIRI	Calcium folinate 50mg/5ml solution for injection vials (Folinic acid)	£52.90
FOLFIRI	Calcium folinate 50mg/5ml solution for injection vials (Folinic acid)	£33.57
FOLFIRI	Fluorouracil 1g/20ml (5%) solution for infusion vials	£8.26
FOLFIRI	Fluorouracil 2.5g/100ml (2.5%) solution for infusion vials	£7.84
FOLFIRI	Fluorouracil 2.5g/50ml (5%) solution for infusion vials	£6.64
FOLFIRI	Fluorouracil 250mg/10ml (2.5%) solution for infusion vials	£138.94
FOLFIRI	Fluorouracil 500mg/10ml (5%) solution for infusion vials	£14.33
FOLFIRI	Fluorouracil 500mg/20ml (2.5%) solution for infusion vials	£96.49
FOLFIRI	Fluorouracil 5g/100ml (5%) solution for infusion	£4.66
FOLFIRI	Irinotecan 100mg/5ml solution for infusion	£23.19
FOLFIRI	Irinotecan 300mg/15ml solution for infusion vials	£19.09
FOLFIRI	Irinotecan 40mg/2ml solution for infusion vials	£39.57
FOLFIRI	Irinotecan 500mg/25ml solution for infusion vials	£16.87
Trifluridine-tipiracil	Trifluridine-tipiracil 20mg	[redacted]
Trifluridine-tipiracil	Trifluridine-tipiracil 15mg	[redacted]

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; mg, milligram; ml, millilitre.
†Model cycle = 30.42 days

Administration costs are included in the model in the form of tablet dispensing costs and vial administration costs as described in Section B.3.5.1.1.3. For FOLFIRI, the vial administration cost is applied every 14 days and for trifluridine-tipiracil the tablet administration cost is applied every 28 days, i.e. at the start of each new treatment cycle.

The total monthly costs for FOLFIRI and trifluridine-tipiracil are shown in Table 52.

Table 52: Primary treatment costs per model cycle for comparators†

Regimen	Drug	Number of options	Average cost across options per model cycle† with RDI	Average cost across options per model cycle† without RDI
FOLFIRI	Folinic acid	7	£24.45	£37.25
	Fluorouracil	7	£39.59	£56.63
	Irinotecan	4	£24.68	£34.04
Trifluridine-tipiracil	Trifluridine-tipiracil	2	[redacted]	[redacted]

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; RDI, relative dose intensity.
†Model cycle = 30.42 days. Number of options = number of treatment formulations available.

B.3.5.1.1.3 Administration costs

Administration costs are included in the model in the form of tablet dispensing costs and vial administration costs.

The tablet dispensing cost was assumed to be £15.29, which was derived by inflating the cost of £13.60 from the trametinib/ dabrafenib company submission for melanoma for NICE TA396 and reported in the ERG report (12 minutes of hospital pharmacist time, hourly rate of hospital pharmacist = £68) (103). The cost was inflated using the values presented in Table 60.

The vial administration cost is assumed to be £233.23 based on NHS Reference costs 2017-2018, Chemotherapy Outpatient (Deliver subsequent elements of a chemotherapy cycle) (104).

A summary of the administration unit costs is shown in Table 53.

Table 53: Treatment administration unit costs

Administration type	Unit cost	Source
Tablet dispensing	£15.29	Trametinib/ dabrafenib for melanoma [TA396], Company Evidence Submission, ERG Report (12 minutes of hospital pharmacist time, hourly rate of hospital pharmacist= £68). Updated to 2017/2018 price level (103).
Vial administration	£233.23	NHS Reference costs 2017-2018, Chemotherapy Outpatient (Deliver Subsequent Elements of a Chemotherapy Cycle) (104).

Abbreviations: NHS, National Health Service; TA, technology appraisal.

For Enco with cetuximab, only the vial administration cost is applied (not the tablet dispensing cost) as only one payment will be issued, and it is assumed that the patient will receive their cetuximab IV treatment and their encorafenib tablets at the same time. In the base-case, cetuximab was assumed to be administered fortnightly in line with CDF

guidance from NHS England (5). An administration cost of £506.72 was incurred every 14 days (Table 54). The cost implications of administering cetuximab once weekly as per the BEACON CRC trial is investigated in a scenario analysis.

Table 54: Enco with cetuximab administration cost calculations

Vial administration unit cost	Frequency per model cycle	Subtotal for 28 days	Adjustment for 30.42 day cycle length
£233.23	2	£466.46	£506.72

As for all other treatment-related costs in the model, the treatment cycle lengths were adjusted to fit the model cycle length of 30.42 days.

The administration cost per cycle for all treatments is shown in Table 55.

Table 55: Total treatment administration costs

	Enco with cetuximab	FOLFIRI	Trifluridine-tipiracil
Cost per model cycle	£506.72	£506.72	£16.61

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan.

B.3.5.1.2 Subsequent treatments

Following discontinuation of the primary treatment, patients switched to a subsequent therapy. The subsequent therapy which patients switched to was determined by their prior treatment and confirmed by expert feedback. Table 56 shows the allocation of subsequent treatments for each arm in the economic model.

Table 56: Subsequent treatments administered in the model based on prior treatment received

Subsequent treatment	Prior treatment			Source
	Enco with cetuximab	FOLFIRI	Trifluridine-tipiracil	
Trifluridine-tipiracil	50%	50%	0%	Clinical expert feedback
BSC	50%	50%	100%	Clinical expert feedback

Abbreviations: BSC, best supportive care; FOLFIRI, folinic acid/fluorouracil/irinotecan.

It was assumed that BSC would be those associated with normal health state resource use for pre- and post-progression; the patients who moved onto BSC after disease progression did not incur any additional treatment costs as a result.

For the patients who moved onto trifluridine-tipiracil following progression, it was assumed that they would receive on average two full cycles of treatment before coming off treatment altogether. This value was sourced from clinical expert opinion due to the dearth of data of subsequent treatments in BRAF V600E mCRC patients.

Table 57: Subsequent treatment costs for patients who progressed onto trifluridine-tipiracil

Parameter	Value	Source
Mean subsequent treatment cycles of trifluridine-tipiracil following progression	2.00	Clinical expert feedback
Conversion from treatment cycles (28 days) to model cycles (30.42 days)	2.17	Calculation
Mean cost per model cycle	£[redacted]	Table 52
Mean administration cost per cycle	£16.61	Table 55
Subtotal per cycle	£[redacted]	Calculation
Total cost of subsequent treatment with trifluridine-tipiracil	**£[redacted]**	**Calculation**

As the costs of subsequent treatments are applied as a one-off cost at the point of progression, only the patients who are estimated to have progressed in that specific model cycle incur the costs. The proportion of patients who would receive treatment with trifluridine-tipiracil after disease progression was used as a weight for the total cost of subsequent treatment with trifluridine-tipiracil, e.g. patients on FOLFIRI would incur £[redacted] * 0.5 = £[redacted] subsequent treatment costs.

B.3.5.2 Health-state unit costs and resource use

The resource costs used for each health state and their associated frequency per cycle are shown in Table 58. Where possible, the latest version of the NHS Schedule of Reference Costs was used (104). The frequency of resource use and the correct sources to use for the corresponding costs were obtained from TA405 table 64 in the company submission (31) and were validated by clinical expert feedback. FOLFIRI patients incurred additional costs relating to peripherally inserted central catheter (PICC) line clearance, which was estimated to be performed once per week to prevent infections and deleterious effects associated with PICC line presence (Clinical expert feedback).

Table 58: List of health states and associated costs in the economic model

Health states	Items	Value	Frequency per model cycle	Source
Pre-progression (non-FOLFIRI regimens)	Oral chemotherapy day case attendance	£163.00	0.50	NHS Schedule of Reference Costs 2017-2018; Daycase and Reg Day/Night, SB11Z, Deliver Exclusively Oral Chemotherapy
	Medical oncologist outpatient consultation	£227.00	0.50	NHS Schedule of Reference Costs 2017-2018; WF02B, Multiprofessional Non-Admitted Face-to-Face Attendance, First, 370, Medical Oncology
	Health home visitor	£46.00	0.50	PSSRU 2019 costs (10.1, Band 6 nurse, page 117); assumed same as district nurse; one hour assumed; without qualification costs
	Total of above (including frequency weights)	£218.00	N/A	Calculation
Pre-progression (FOLFIRI)	Oral chemotherapy day case attendance	£163.00	0.50	NHS Schedule of Reference Costs 2017-2018; Daycase and Reg Day/Night, SB11Z, Deliver Exclusively Oral Chemotherapy
	Medical oncologist outpatient consultation	£227.00	0.50	NHS Schedule of Reference Costs 2017-2018; WF02B, Multiprofessional Non-Admitted Face-to-Face Attendance, First, 370, Medical Oncology
	Health home visitor	£46.00	4.00	PSSRU 2019 costs (10.1, Band 6 nurse, page 117); assumed same as district nurse; one hour assumed; without qualification costs
	District nurse visit for PICC line flushing	£46.00	4.00	PSSRU 2019 costs (10.1, Band 6 nurse, page 117); one hour assumed; without qualification costs
	Total of above (including frequency weights)	£402.00	N/A	Calculation
Post-progression	GP home consultation	£100.46	0.25	TA405-PSSRU 2015 costs uprated to 2017/8 using PSSRU CPI health; one hour assumed
	Community nurse specialist visit	£37.00	1.00	PSSRU 2019 costs (10.2, Nurse (GP practice), page 118); one hour assumed; without qualification costs
	Health home visitor	£46.00	4.00	PSSRU 2019 costs (10.1, Band 6 nurse, page 117); assumed same as district nurse; one hour assumed; without qualification costs
	District nurse visit	£46.00	4.00	PSSRU 2019 costs (10.1, Band 6 nurse, page 117); one hour assumed; without qualification costs
	GP surgery visit	£28.16	1.00	PSSRU 2019 costs (10.3b, General practitioner, per patient consultation

Health states	Items	Value	Frequency per model cycle	Source
				lasting 9.22 minutes, excluding direct care staff costs, without qualification costs, page 120)
	Total of above (including frequency weights)	£182.28	N/A	Calculation

Abbreviations: FOLFIRI, folinic acid/fluorouracil/irinotecan; GP, general practitioner; N/A, not applicable; PFS, progression-free survival; PICC, peripherally inserted central catheter; PSSRU, Personal Social Services Research Unit.

B.3.5.3 Adverse reaction unit costs and resource use

The costs of AEs were primarily sourced from previous NICE TAs. Where possible, the latest version of the NHS Schedule of Reference Costs was used (104). Where it was not clear how the cost was originally derived, the cost was inflated from its cost year to 2018/2019 values using the inflation indices shown in Table 60. When no cost could be identified for an AE, the mean cost of all other AEs excluding neutropenia, liver injury and febrile neutropenia were used. The neutropenia, liver injury and febrile neutropenia costs were excluded from the estimated AE cost as these events have high costs associated with them and inclusion of these costs as components of the average AE cost may have resulted in an overestimation of AE costs.

Table 59: List of AEs and summary of costs in the economic model

AE	Items	Value	Source
Abdominal pain	Total unit cost	£144.79	NHS Reference costs 2017-2018, total outpatient attendances, pain management, total unit cost, service code 191 (as applied in TA405 Trifluridine/Tipiracil)
Anaemia	N/A	£0.00	Advised to not include AE cost as per KOL feedback
Asthenia	Total unit cost	£163.58	NHS Reference costs 2017-2018, total outpatient attendances, general medicine, total unit cost (as applied in TA405 table 67)
Cancer pain	Total unit cost	£144.79	NHS Reference costs 2017-2018, total outpatient attendances, pain management, total unit cost, service code 191 (as applied in TA405 table 67)
Decreased appetite	N/A	£0.00	Advised to not include AE cost as per KOL feedback
Diarrhoea	Total unit cost	£163.58	NHS Reference costs 2017-2018, total outpatient attendances, general medicine, total unit cost (as applied in TA405 Trifluridine/Tipiracil)
Fatigue	Total unit cost	£163.58	NHS Reference costs 2017-2018, total outpatient attendances, general medicine, total unit cost (as applied in TA405 Trifluridine/Tipiracil)
Febrile neutropenia	Total unit cost	£2,806.66	NICE DSU Report, inflated to 2018/2019 costs using PSSRU HCHS / NHSCII indices, as per TA405

AE	Items	Value	Source
Hypertension	Total unit cost	£879.97	TA307 inflated to 2018/2019 costs using PSSRU HCHS / NHSCII indices
Intestinal obstruction	Total unit cost	£215.95	Cost not identified; average of all known AEs taken excluding neutropenia, febrile neutropenia, leukopenia and liver injury
Leukopenia	Estimated unit cost	£2,504.27	Assumed same as neutropenia
Liver injury/ failure	Total unit cost	£2,887.00	NHS Reference costs 2017-2018, total HRGs, weighted average of currency codes GC01C, GC01D and GC01E (liver failure disorders).
Nausea	Total unit cost	£0.00	Advised to not include AE cost as per KOL feedback
Neutropenia	Total unit cost	£2,504.27	TA439 ERG report table 127 value for neutropenia used and inflated to 2018/2019 costs using PSSRU HCHS / NHSCII indices
Stomatitis	Total unit cost	£163.58	NHS Reference costs 2017-2018, total outpatient attendances, general medicine, total unit cost (as applied in TA405 Trifluridine/Tipiracil)
Thrombocytopenia	Total unit cost	£640.09	NHS Reference costs 2017-2018, total HRGs, weighted average of currency codes SA12G, SA12H, SA12J and SA12K (thrombocytopenia).
Urinary tract infection	Estimated unit cost	£215.95	Cost not identified; average of all known AEs taken excluding neutropenia, febrile neutropenia, leukopenia and liver injury
Venous thrombosis	Estimated unit cost	£215.95	Cost not identified; average of all known AEs taken excluding neutropenia, febrile neutropenia, leukopenia and liver injury
Vomiting	Total unit cost	£163.58	NHS Reference costs 2017-2018, total outpatient attendances, general medicine, total unit cost (as applied in TA405 Trifluridine/Tipiracil)

Abbreviations: AE, adverse event; ERG, Evidence Review Group; HCHS, Health Sector Cost Index; N/A, not applicable; NHSCII, NHS Cost Inflation Index; PSSRU, Personal Social Services Research Unit; TA, Technology Assessment.

B.3.5.4 Terminal care costs

The costs associated with terminal care and patient death were sourced from a study which estimated the costs of caring for CRC patients at the end of life as previously used in TA405 (105). The costs calculated in this study included health and social care requirements and excluded the costs of informal care. The total cost for end-of-life care was reported to be £6,910 (2015 GBP). This cost was inflated to 2018/2019 values using Table 60.

B.3.5.5 Inflation methods

Inflation of values from previous cost years was performed using Table 60, adapted from the PSSRU Unit Costs of Health & Social Care 2019 (106). For all costs, the prices index was used for any inflations performed.

Table 60: Inflation percent changes used to inflate costs in the economic model

Year	Index	Prices	Pay	Pay and prices
2009	HCHS	-1.30%	1.80%	0.60%
2010	HCHS	2.80%	3.10%	3.00%
2011	HCHS	4.10%	0.90%	2.10%
2012	HCHS	3.10%	0.90%	1.70%
2013	HCHS	1.80%	0.70%	1.10%
2014	HCHS	1.70%	0.30%	0.90%
2015	HCHS	2.70%	0.30%	1.30%
2016	NHSCII	2.16%	2.10%	2.12%
2017	NHSCII	1.07%	1.22%	1.16%
2018	NHSCII	2.43%	2.24%	2.31%

Abbreviations: HCHS, Hospital and Community Health Services; NHSCII, NHS Cost Inflation Index

B.3.5.6 Summary of costs included in the analysis

A top-level summary of the costs described in the previous sections across all treatment arms is described in Table 61.

Table 61: Summary of costs used in the model by treatment arm

	Enco with cetuximab		FOLFIRI		Trifluridine-tipiracil	
Items	**Cost**	**Reference in submission**	**Cost**	**Reference in submission**	**Cost**	**Reference in submission**
Premedication costs	£15	Table 45	£0	N/A	£0	N/A
Loading dose	£1,084	B.3.5.1.1.1	N/A	N/A	N/A	N/A
Treatment cost/ cycle	[redacted]	B.3.5.1.1.1	£89	B.3.5.1.1.2	£[redacted]	B.3.5.1.1.2
Administration cost	£507	B.3.5.1.1.3	£507	B.3.5.1.1.3	£17	B.3.5.1.1.3
Total first cycle	[redacted]	B.3.5.1.1.1	£89	B.3.5.1.1.2	£[redacted]	B.3.5.1.1.2
Total subsequent cycles	[redacted]	B.3.5.1.1.1	£89	B.3.5.1.1.2	£[redacted]	B.3.5.1.1.2
Pre-progression cost per cycle	£218	B.3.5.2	£402	B.3.5.2	£218	B.3.5.2
Post-progression cost per cycle	£182	B.3.5.2	£182	B.3.5.2	£182	B.3.5.2
Terminal care costs	£7,162	B.3.5.4	£7,162	B.3.5.4	£7,162	B.3.5.4
Subsequent treatment cost on progression	£1,936	B.3.5.1.2	£1,936	B.3.5.1.2	£0	B.3.5.1.2
AE total costs applied in first cycle	£84	B.3.5.3	£443	B.3.5.3	£1,078	B.3.5.3

Abbreviations: AE, adverse event; FOLFIRI, folinic acid/fluorouracil/irinotecan; N/A, not applicable.

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

B.3.6.1 Summary of base-case analysis inputs

The base-case inputs for the economic model are presented in Table 62. For conciseness, only the main variables are shown (i.e. for treatment costs the mg per tablet/ vial and the number of tablets/ vials per pack are shown in the variable name and are not listed as a separate value).

Table 62: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model setup parameters			
Discount rate (costs)	3.5%	PSA: Fixed DSA: 0%-6%	Section B.3.2.2.2
Discount rate (QALYs)	3.5%	PSA: Fixed DSA: 0%-6%	Section B.3.2.2.2
Age; mean	59.3 years	SE: 0.458 (Normal)	Section B.3.2.1
Sex (male)	47.2%	N=665, alpha = 314 (Beta)	Section B.3.2.1
BSA (m^2); mean	1.79	SE: 0.009 (Normal)	Section B.3.2.1
HRs			
FOLFIRI PFS HR; median	3.333	LCI: 1.47, UCI: 7.14 (Lognormal)	Section B.3.3.1.3.1
FOLFIRI OS HR; median	2.564	LCI: 1.23, UCI: 5.26 (Lognormal)	Section B.3.3.1.3.1
Trifluridine-tipiracil BRAF adjustment HR for PFS; median	3.571	LCI: 2.50, UCI: 5.00 (Lognormal)	Section B.3.3.1.4.3
Trifluridine-tipiracil BRAF adjustment HR for OS; median	4.000	LCI: 2.78, UCI: 5.56 (Lognormal)	Section B.3.3.1.4.3
Base-case survival curve parameters			
Enco with cetuximab PFS distribution	Loglogistic	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.1.2.1
Enco with cetuximab OS distribution	Loglogistic	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.1.2.1
FOLFIRI PFS distribution (not used in base-case)	Loglogistic	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.1.3.2
FOLFIRI OS distribution (not used in base-case)	Loglogistic	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.1.3.2
Trifluridine-tipiracil PFS distribution	Loglogistic	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.1.4.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Trifluridine-tipiracil OS distribution	Loglogistic	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.1.4.2
Adverse event rates			
Abdominal pain rate, Enco with cetuximab	3.24%	N= 216, alpha = 7 (Beta)	Section B.3.3.2
Anaemia rate, Enco with cetuximab	[redacted]	N= 216, alpha = 12 (Beta)	Section B.3.3.2
Asthenia rate, Enco with cetuximab	3.70%	N= 216, alpha = 8 (Beta)	Section B.3.3.2
Cancer pain rate, Enco with cetuximab	2.31%	N= 216, alpha = 5 (Beta)	Section B.3.3.2
Decreased appetite rate, Enco with cetuximab	[redacted]	N= 216, alpha = 3 (Beta)	Section B.3.3.2
Diarrhoea rate, Enco with cetuximab	2.78%	N= 216, alpha = 6 (Beta)	Section B.3.3.2
Fatigue rate, Enco with cetuximab	4.17%	N= 216, alpha = 9 (Beta)	Section B.3.3.2
Febrile neutropenia rate, Enco with cetuximab	[redacted]	N/A (Fixed)	Section B.3.3.2
Hypertension rate, Enco with cetuximab	[redacted]	N= 216, alpha = 3 (Beta)	Section B.3.3.2
Intestinal obstruction rate, Enco with cetuximab	4.63%	N= 216, alpha = 10 (Beta)	Section B.3.3.2
Leukopenia rate, Enco with cetuximab	[redacted]	N/A (Fixed)	Section B.3.3.2
Liver injury / failure rate, Enco with cetuximab	[redacted]	N/A (Fixed)	Section B.3.3.2
Nausea rate, Enco with cetuximab	0.00%	N/A (Fixed)	Section B.3.3.2
Neutropenia rate, Enco with cetuximab	[redacted]	N= 216, alpha = 2 (Beta)	Section B.3.3.2
Stomatitis rate, Enco with cetuximab	[redacted]	N/A (Fixed)	Section B.3.3.2
Thrombocytopenia rate, Enco with cetuximab	[redacted]	N/A (Fixed)	Section B.3.3.2
Urinary tract infection rate, Enco with cetuximab	2.31%	N= 216, alpha = 5 (Beta)	Section B.3.3.2
Venous thrombosis rate, Enco with cetuximab	[redacted]	N= 216, alpha = 0 (Beta)	Section B.3.3.2
Vomiting rate, Enco with cetuximab	1.39%	N= 216, alpha = 3 (Beta)	Section B.3.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Abdominal pain rate, FOLFIRI	3.60%	N = 528, alpha = 19 (Beta)	Section B.3.3.2
Anaemia rate, FOLFIRI	3.60%	N= 528, alpha = 19 (Beta)	Section B.3.3.2
Asthenia rate, FOLFIRI	0.00%	N/A (Fixed)	Section B.3.3.2
Cancer pain rate, FOLFIRI	0.00%	N/A (Fixed)	Section B.3.3.2
Decreased appetite rate, FOLFIRI	1.89%	N= 528, alpha = 10 (Beta)	Section B.3.3.2
Diarrhoea rate, FOLFIRI	9.66%	N= 528, alpha = 51 (Beta)	Section B.3.3.2
Fatigue rate, FOLFIRI	7.77%	N= 528, alpha = 41 (Beta)	Section B.3.3.2
Febrile neutropenia rate, FOLFIRI	2.46%	N=528, alpha = 13 (Beta)	Section B.3.3.2
Hypertension rate, FOLFIRI	2.84%	N= 528, alpha = 15 (Beta)	Section B.3.3.2
Intestinal obstruction rate, FOLFIRI	0.00%	N/A (Fixed)	Section B.3.3.2
Leukopenia rate, FOLFIRI	2.65%	N= 528, alpha = 14 (Beta)	Section B.3.3.2
Liver injury / failure rate, FOLFIRI	3.98%	N= 528, alpha = 21 (Beta)	Section B.3.3.2
Nausea rate, FOLFIRI	2.65%	N= 528, alpha = 14 (Beta)	Section B.3.3.2
Neutropenia rate, FOLFIRI	23.30%	N= 528, alpha = 123 (Beta)	Section B.3.3.2
Stomatitis rate, FOLFIRI	2.27%	N= 528, alpha = 12 (Beta)	Section B.3.3.2
Thrombocytopenia rate, FOLFIRI	0.76%	N= 528, alpha = 4 (Beta)	Section B.3.3.2
Urinary tract infection rate, FOLFIRI	0.00%	N/A (Fixed)	Section B.3.3.2
Venous thrombosis rate, FOLFIRI	2.08%	N= 528, alpha = 11 (Beta)	Section B.3.3.2
Vomiting rate, FOLFIRI	2.46%	N= 528, alpha = 13 (Beta)	Section B.3.3.2
Abdominal pain rate, Trifluridine-tipiracil	2.44%	N = 533, alpha = 13 (Beta)	Section B.3.3.2
Anaemia rate, Trifluridine-tipiracil	18.18%	N= 528, alpha = 96 (Beta)	Section B.3.3.2
Asthenia rate, Trifluridine-tipiracil	3.38%	N= 533, alpha = 18 (Beta)	Section B.3.3.2
Cancer pain rate, Trifluridine-tipiracil	0.00%	N/A (Fixed)	Section B.3.3.2
Decreased appetite rate, Trifluridine-tipiracil	3.56%	N= 533, alpha = 19 (Beta)	Section B.3.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Diarrhoea rate, Trifluridine-tipiracil	3.00%	N= 533, alpha = 16 (Beta)	Section B.3.3.2
Fatigue rate, Trifluridine-tipiracil	3.94%	N= 533, alpha = 21 (Beta)	Section B.3.3.2
Febrile neutropenia rate, Trifluridine-tipiracil	3.75%	N=533, alpha = 20 (Beta)	Section B.3.3.2
Hypertension rate, Trifluridine-tipiracil	0.00%	N/A (Fixed)	Section B.3.3.2
Intestinal obstruction rate, Trifluridine-tipiracil	0.00%	N/A (Fixed)	Section B.3.3.2
Leukopenia rate, Trifluridine-tipiracil	21.40%	N= 533, alpha = 113 (Beta)	Section B.3.3.2
Liver injury / failure rate, Trifluridine-tipiracil	0.00%	N/A (Fixed)	Section B.3.3.2
Nausea rate, Trifluridine-tipiracil	0.00%	N/A (Fixed)	Section B.3.3.2
Neutropenia rate, Trifluridine-tipiracil	37.88%	N= 528, alpha = 200 (Beta)	Section B.3.3.2
Stomatitis rate, Trifluridine-tipiracil	0.00%	N/A (Fixed)	Section B.3.3.2
Thrombocytopenia rate, Trifluridine-tipiracil	5.11%	N= 528, alpha = 27 (Beta)	Section B.3.3.2
Urinary tract infection rate, Trifluridine-tipiracil	0.00%	N= 533, alpha = 0 (Beta)	Section B.3.3.2
Venous thrombosis rate, Trifluridine-tipiracil	0.00%	N= 533, alpha = 0 (Beta)	Section B.3.3.2
Vomiting rate, Trifluridine-tipiracil	2.06%	N= 533, alpha = 11 (Beta)	Section B.3.3.2
Treatment costs			
Calcium folinate 100mg/10ml solution for injection vials (Folinic acid) / Pack size 1 cost	£2.40	SE: £0.05, (Gamma)	Section B.3.5.1.1.2
Calcium folinate 100mg/10ml solution for injection vials (Folinic acid) / Pack size 10 cost	£11.84	SE: £0.51, (Gamma)	Section B.3.5.1.1.2
Calcium folinate 300mg/30ml solution for injection vials (Folinic acid) / Pack size 1 cost	£3.71	SE: £0.06, (Gamma)	Section B.3.5.1.1.2
Calcium folinate 350mg/35ml solution for injection vials (Folinic acid) / Pack size 1 cost	£5.36	SE: £0.02, (Gamma)	Section B.3.5.1.1.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Calcium folinate 350mg/35ml solution for injection vials (Folinic acid) / Pack size 10 cost	£49.98	SE: £0.01, (Gamma)	Section B.3.5.1.1.2
Calcium folinate 50mg/5ml solution for injection vials (Folinic acid) / Pack size 1 cost	£2.43	SE: £0.03, (Gamma)	Section B.3.5.1.1.2
Calcium folinate 50mg/5ml solution for injection vials (Folinic acid) / Pack size 10 cost	£15.42	SE: £0.50, (Gamma)	Section B.3.5.1.1.2
Fluorouracil 1g/20ml (5%) solution for infusion vials / Pack size 1 cost	£1.13	SE: £0.00, (Gamma)	Section B.3.5.1.1.2
Fluorouracil 2.5g/100ml (2.5%) solution for infusion vials / Pack size 1 cost	£2.68	SE: £0.04, (Gamma)	Section B.3.5.1.1.2
Fluorouracil 2.5g/50ml (5%) solution for infusion vials / Pack size 1 cost	£2.27	SE: £0.01, (Gamma)	Section B.3.5.1.1.2
Fluorouracil 250mg/10ml (2.5%) solution for infusion vials / Pack size 5 cost	£23.76	SE: £0.44, (Gamma)	Section B.3.5.1.1.2
Fluorouracil 500mg/10ml (5%) solution for infusion vials / Pack size 1 cost	£0.98	SE: £0.05, (Gamma)	Section B.3.5.1.1.2
Fluorouracil 500mg/20ml (2.5%) solution for infusion vials / Pack size 10 cost	£66.00	SE: £0.28, (Gamma)	Section B.3.5.1.1.2
Fluorouracil 5g/100ml (5%) solution for infusion vials / Pack size 1 cost	£3.19	SE: £0.00, (Gamma)	Section B.3.5.1.1.2
Irinotecan 100mg/5ml solution for infusion vials / Pack size 1 cost	£4.60	SE: £0.04, (Gamma)	Section B.3.5.1.1.2
Irinotecan 300mg/15ml solution for infusion vials / Pack size 1 cost	£11.36	SE: £0.18, (Gamma)	Section B.3.5.1.1.2
Irinotecan 40mg/2ml solution for infusion vials / Pack size 1 cost	£3.14	SE: £0.03, (Gamma)	Section B.3.5.1.1.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Irinotecan 500mg/25ml solution for infusion vials / Pack size 1 cost	£16.73	SE: £0.01, (Gamma)	Section B.3.5.1.1.2
Trifluridine-tipiracil 20mg tablets / pack size 60 cost	[redacted]	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.1.1.2
Trifluridine-tipiracil 15mg tablets / pack size 60 cost	[redacted]	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.1.1.2
Encorafenib 75mg tablets / pack size 42 cost	£579.62	No variance assumed (Fixed)	Section B.3.5.1.1.1
Cetuximab 500mg vial / pack size 1 cost	£890.50	No variance assumed (Fixed)	Section B.3.5.1.1.1
Chlorphenamine 10mg/1ml solution for injection ampoules / Pack size 5 cost	£12.14	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.1.1.1
Hydrocortisone sodium succinate 100mg powder for solution for injection vials (e.g. Solu-Cortef or eqv) / Pack size 10 cost	£9.09	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.1.1.1
Paracetamol 500mg tablets / Pack size 16 cost	£0.11	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.1.1.1
Drug administration costs			
Tablet dispensing cost	£15.29	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.1.1.3
Vial administration cost	£233.23	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.1.1.3
Adverse event costs			
Abdominal pain	£144.79	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Anaemia	£0.00	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Asthenia	£163.58	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Cancer pain	£144.79	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Decreased appetite	£0.00	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Diarrhoea	£163.58	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Fatigue	£163.58	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Febrile neutropenia	£2,806.66	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Hypertension	£879.97	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Intestinal obstruction	£215.95	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Leukopenia	£2,504.27	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Liver injury / failure	£2,887.00	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Nausea	£0.00	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Neutropenia	£2,504.27	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Stomatitis	£163.58	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Thrombocytopenia	£640.09	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Urinary tract infection	£215.95	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Venous thrombosis	£215.95	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3
Vomiting	£163.58	No variance data available; SE assumed as 10% of the mean, (Gamma)	Section B.3.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Relative dose intensities			
Calcium folinate (all formulations) RDI	0.716	SE: 0.025 (Normal)	Section B.2.11.1.1
Fluorouracil (all formulations) RDI	0.673	SE: 0.025 (Normal)	Section B.2.11.1.1
Irinotecan (all formulations) RDI	0.725	SE: 0.017 (Normal)	Section B.2.11.1.1
Trifluridine-tipiracil (all formulations) RDI	1.000	No variance data available; SE assumed as 10% of the mean (Normal)	N/A
Encorafenib RDI	[redacted]	SE: 0.013 (Normal)	Section B.2.11.1.1
Cetuximab RDI	[redacted]	SE: 0.010 (Normal)	Section B.2.11.1.1
Resource use costs			
Oral chemotherapy day case attendance cost	£163.00	No variance data available; SE assumed as 10% of the mean (Gamma)	Section B.3.5.2
Medical oncologist outpatient consultation cost	£227.00	No variance data available; SE assumed as 10% of the mean (Gamma)	Section B.3.5.2
GP home consultation cost	£100.46	No variance data available; SE assumed as 10% of the mean (Gamma)	Section B.3.5.2
Community nurse specialist visit cost	£37.00	No variance data available; SE assumed as 10% of the mean (Gamma)	Section B.3.5.2
Health home visitor cost	£46.00	No variance data available; SE assumed as 10% of the mean (Gamma)	Section B.3.5.2
District nurse visit (PICC line care) cost	£46.00	No variance data available; SE assumed as 10% of the mean (Gamma)	Section B.3.5.2
GP surgery visit cost	£28.16	No variance data available; SE assumed as 10% of the mean (Gamma)	Section B.3.5.2
Terminal case costs			
Terminal care cost	£7,162.14	No variance data available; SE assumed as 10% of the mean (Gamma)	Section B.3.5.4
Resource use rates			
Oral chemotherapy day case attendance rate, pre-progression	0.50	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2
Medical oncologist outpatient consultation rate, pre-progression	0.50	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Health home visitor rate, pre-progression	0.50	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2
GP home consultation rate, post-progression disease	0.25	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2
Community nurse specialist visit rate, post-progression	1.00	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2
Health home visitor rate, post-progression	1.00	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2
GP surgery visit, post-progression	1.00	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2
District nurse visit (PICC line care) rate, post-progression	1.00	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2
District nurse visit (PICC line care) rate, pre-progression, FOLFIRI only	4.00	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.2
Subsequent treatment costs			
Enco with cetuximab proportion progressing to trifluridine-tipiracil	50%	No variance data available; SE assumed as 10% of the mean (Beta)	Section B.3.5.1.2
FOLFIRI proportion progressing to trifluridine-tipiracil	50%	No variance data available; SE assumed as 10% of the mean (Beta)	Section B.3.5.1.2
Mean subsequent treatment cycles with trifluridine-tipiracil	2.00	No variance data available; SE assumed as 10% of the mean (Normal)	Section B.3.5.1.2
Utility values			
Enco with cetuximab, pre-progression	0.743	SE: 0.005 (Beta)	Section B.3.4.1/ B.3.4.5
Enco with cetuximab, post-progression	0.622	SE: 0.021 (Beta)	Section B.3.4.1/ B.3.4.5
FOLFIRI, pre-progression	0.741	SE: 0.008 (Beta)	Section B.3.4.1/ B.3.4.5
FOLFIRI, post-progression	0.631	SE: 0.022 (Beta)	Section B.3.4.1/ B.3.4.5
Trifluridine-tipiracil, pre-progression	0.742	N/A; mean of Enco with cetuximab and FOLFIRI pre-progression utility	Section B.3.4.1/ B.3.4.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Trifluridine-tipiracil, post-progression	0.627	N/A; mean of Enco with cetuximab and FOLFIRI post-progression utility	Section B.3.4.1/ B.3.4.5

Abbreviations: BSA, body surface area; CI, confidence interval; DSA, deterministic sensitivity analysis; FOLFIRI, Folinic acid/fluorouracil/irinotecan; HR, hazard ratio; LCI, lower confidence interval; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PICC, peripherally inserted central catheter; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; RDI, relative dose intensity; SE, standard error; UCI, upper confidence interval.

B.3.6.2 Assumptions

The assumptions used to generate the base-case of the model are shown in Table 63. A brief summary of the most impactful assumptions is listed in the bullet points below.

- OS and PFS curves: BEACON CRC IPD for Enco with cetuximab, ITC HR applied for FOLFIRI; digitised curves for non-BRAF-mutant study used for trifluridine-tipiracil.
- OS and PFS extrapolations: Loglogistic parametric curves for both curves.
- TTD: Equal to PFS.
- Trifluridine-tipiracil survival curves: adjusted by HR for BRAF wild-type vs BRAF-mutant.
- Utilities: BEACON individual arms utilised for Enco with cetuximab and FOLFIRI, average across BEACON arms used for trifluridine-tipiracil.

Table 63: List of assumptions used in the economic model

Assumption	Justification
Time horizon: 10 years	Clinical expert feedback; no patients would be expected to be alive beyond 10 years.
Half-cycle correction: enabled	The cycle length and short time horizon of the model requires that half-cycle correction is implemented.
Time to discontinuation: equivalent to PFS	No statistically significant difference was identified between the PFS and TTD curves for either the BEACON CRC Enco with cetuximab or control arm. This was corroborated by clinical expert feedback, where the consensus was that patients would be expected to remain on treatment whilst they were progression-free.
Choice of parametric model for survival curves	Clinical expert views were mixed between the loglogistic and Weibull distributions; the loglogistic curve was deemed more appropriate based on AIC and visual inspection. Loglogistic was used in the base-case. Weibull models were explored in scenario analyses.
Efficacy approach for FOLFIRI: utilises results of grouped treatment nodes ITC	The ITC enabled Enco with cetuximab and FOLFIRI to be compared via a grouped treatment nodes approach described in Section B.2.10. In contrast to the BEACON CRC study where cetuximab was included in the FOLFIRI/irinotecan control arm, the ITC allowed evidence for FOLFIRI when administered alone to be incorporated into the evidence network. The ITC represents the best available evidence to estimate the relative

Assumption	Justification
	effectiveness of the encorafenib regimen versus FOLFIRI, using a validated statistical approach.
Efficacy approach for trifluridine-tipiracil: trifluridine-tipiracil OS and PFS K-M curves sourced from the RECOURSE trial (Mayer 2015) followed by adjustment by application of BRAF-mutant versus wild-type HRs (Peeters 2015)	The trifluridine-tipiracil trial (RECOURSE) was conducted in a population for which BRAF status was not reported (66). Based on the RAS-status of patients in the study and epidemiology data it is expected that the majority of patients would have been BRAF wild-type (Section B.2.10.5. Patients with BRAF-mutant mCRC have a substantially poorer prognosis than patients with BRAF wild-type, and as such BRAF wild-type data would significantly overestimate the effectiveness of trifluridine-tipiracil in a BRAF-mutant population. To account for this the RECOURSE K-M survival curves were adjusted using published HRs for OS and PFS for BRAF wild-type versus BRAF-mutant. This was corroborated by expert feedback.
AEs: Grade 3+ AEs sourced directly from relevant RCTs for each intervention and comparator	AEs for Enco with cetuximab were taken from the Enco with cetuximab arm of BEACON CRC. Although the control arm of BEACON CRC could have been used as a proxy for AEs observed with FOLFIRI, the control arm did consist of FOLFIRI or irinotecan in combination with cetuximab. To attempt to more accurately model the AE profile of FOLFIRI when taken alone (as per the NICE scope), AEs were sourced from a large Phase 3 RCT which compared ramucirumab with FOLFIRI versus FOLFIRI alone in patients with mCRC (RAISE). A similar approach was taken for trifluridine-tipiracil using data from the RECOURSE study.
Vial wastage/ sharing: vial sharing assumed	Clinical expert feedback that vial sharing would occur wherever possible in order to minimise costs.
Subsequent treatment duration: two cycles of trifluridine-tipiracil	There were no data available for time to discontinuation in patients whose disease had progressed and were on trifluridine-tipiracil. Expert feedback was sought to determine the mean number of cycles a patient would undergo until cessation of treatment or death.
Utility values: treatment arm-specific EQ-5D derived from BEACON CRC	Whilst no statistically significant difference between utilities by treatment arm was observed in the BEACON trial, as the data and probability distributions were available by treatment arm, the decision was taken to use the data in the most granular format possible.
Utility values: coupling of treatment status and pre-progression/ post-progression health states	As there was no statistically significant difference between PFS and TTD in the model, it was assumed that time points before “end of treatment” (excluding screening) were equivalent to being in the “pre-progression” health state, and time points beyond and including “end of treatment” were equivalent to being in the “post-progression” health state.
Utility values: adjustment of general population utilities for age and sex	An age and sex-related decline in overall general population utility was assumed as per the methods described in Section B.3.4.5.3 and Ara and Brazier 2010 (96).

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; FOLFIRI, folinic acid/fluorouracil/irinotecan; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.3.7 Base-case results

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

The base-case results are presented in Table 64. Clinical outcomes from the model are provided in Appendix J. Disaggregated results of the base-case cost-effectiveness analysis are provided in Appendix J.

All results are based on cetuximab list price and do not take account of the confidential commercial discount that would be applicable to combination treatment with Enco in the mCRC setting. As such, these results are not representative of the true cost-effectiveness estimates anticipated.

Table 64: Base-case deterministic cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FOLFIRI	£12,204	0.59	0.40					
Trifluridine-tipiracil	[redacted]	0.38	0.26	[redacted]	-0.21	-0.14	Dominated	Dominated
Enco with cetuximab	[redacted]	1.36	0.92	[redacted]	0.78	0.52	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The PSA was run by simultaneously sampling from probability distributions for all variables included in the model and generating costs and QALYs for each treatment arm. The PSA convergence tool described in Hatswell 2018 (107) was used to determine the number of simulations required to reach convergence; convergence was determined when the upper and lower confidence interval limits of the net monetary benefit for Enco with cetuximab versus FOLFIRI did not cross zero.

Using this method, 1,000 simulations was determined to be a sufficient number of simulations to generate robust estimates of cost-effectiveness.

The PSA results are presented in Table 65. Pairwise cost-effectiveness frontiers are presented in Figure 19 and Figure 20 for Enco with cetuximab versus FOLFIRI and Enco with cetuximab versus trifluridine-tipiracil respectively.

All results are based on cetuximab list price and do not take account of the confidential commercial discount that would be applicable to combination treatment with Enco in the mCRC setting. As such, these results are not representative of the true cost-effectiveness estimates anticipated.

Table 65: Base-case probabilistic cost-effectiveness results

Technologies	Total costs (£), SD	Total LYG, SD	Total QALYs, SD	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FOLFIRI	£12,434 (801)	0.632 (0.19)	0.431 (0.12)					
Trifluridine-tipiracil	[redacted]	0.379 (0.03)	0.260 (0.02)	[redacted]	-0.253	-0.172	Dominated	Dominated
Enco with cetuximab	[redacted]	1.372 (0.12)	0.923 (0.07)	[redacted]	0.739	0.492	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; SD, standard deviation; QALYs, quality-adjusted life years.

Figure 19: CE plane: Enco with cetuximab versus FOLFIRI

Abbreviations: CE, cost-effectiveness; FOLFIRI, Folinic acid/fluorouracil/irinotecan; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 20: CE plane: Enco with cetuximab versus trifluridine-tipiracil

Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

The probability of Enco with cetuximab being cost-effective at a willingness-to-pay threshold of £50,000/ QALY was approximately 1% as shown in Figure 21.

Figure 21: Cost-effectiveness acceptability curve

B.3.8.2 Deterministic sensitivity analysis

Pairwise deterministic sensitivity analyses are presented below. Some variables were not included in the DSA; these include:

- Discount rates, as per the NICE reference case.
- Parametric model parameters, as these values have a joint distribution with one another, so changing one variable whilst not changing the others will generate implausible survival estimates.
- Other values which are otherwise fixed, such as doses (mg per m^2).

The values which were included in the DSA were varied by +/-10%. A list of the included variables is presented in Table 66.

All results are based on cetuximab list price and do not take account of the confidential commercial discount that would be applicable to combination treatment with Enco in the mCRC setting. As such, these results are not representative of the true cost-effectiveness estimates anticipated.

Table 66: DSA inputs used

Variable	Base-case value	Low estimate	High estimate
Mean age at baseline	59.30	53.37	65.23
Proportion male	0.47	0.42	0.52
Mean BSA	1.79	1.61	1.97
OS HR for mortality; FOLFIRI	2.56	2.31	2.82
pre-progression HR for mortality; FOLFIRI	3.33	3.00	3.67
OS HR for mortality; trifluridine/tipiracil	4.00	3.60	4.40
pre-progression HR for mortality; trifluridine/tipiracil	3.57	3.21	3.93
Enco with cetuximab pre-progression utility	0.74	0.67	0.82
FOLFIRI pre-progression utility	0.74	0.67	0.81
Enco with cetuximab post-progression utility	0.62	0.56	0.68
FOLFIRI post-progression utility	0.63	0.57	0.69
Calcium folinate 100mg/10ml solution for injection vials (Folinic acid) / Pack size 1	£2.40	£2.16	£2.64
Calcium folinate 100mg/10ml solution for injection vials (Folinic acid) / Pack size 10	£11.84	£10.66	£13.02
Calcium folinate 300mg/30ml solution for injection vials (Folinic acid) / Pack size 1	£3.71	£3.34	£4.08
Calcium folinate 350mg/35ml solution for injection vials (Folinic acid) / Pack size 1	£5.36	£4.82	£5.90
Calcium folinate 350mg/35ml solution for injection vials (Folinic acid) / Pack size 10	£49.98	£44.98	£54.98
Calcium folinate 50mg/5ml solution for injection vials (Folinic acid) / Pack size 1	£2.43	£2.19	£2.67
Calcium folinate 50mg/5ml solution for injection vials (Folinic acid) / Pack size 10	£15.42	£13.88	£16.96
Fluorouracil 1g/20ml (5%) solution for infusion vials / Pack size 1	£1.13	£1.02	£1.24
Fluorouracil 2.5g/100ml (2.5%) solution for infusion vials / Pack size 1	£2.68	£2.41	£2.95
Fluorouracil 2.5g/50ml (5%) solution for infusion vials / Pack size 1	£2.27	£2.04	£2.50
Fluorouracil 250mg/10ml (2.5%) solution for infusion vials / Pack size 5	£23.76	£21.38	£26.14
Fluorouracil 500mg/10ml (5%) solution for infusion vials / Pack size 1	£0.98	£0.88	£1.08
Fluorouracil 500mg/20ml (2.5%) solution for infusion vials / Pack size 10	£66.00	£59.40	£72.60
Fluorouracil 5g/100ml (5%) solution for infusion vials / Pack size 1	£3.19	£2.87	£3.51
Irinotecan 100mg/5ml solution for infusion vials / Pack size 1	£4.60	£4.14	£5.06
Irinotecan 300mg/15ml solution for infusion vials / Pack size 1	£11.36	£10.22	£12.50
Irinotecan 40mg/2ml solution for infusion vials / Pack size 1	£3.14	£2.83	£3.45

Variable	Base-case value	Low estimate	High estimate
Irinotecan 500mg/25ml solution for infusion vials / Pack size 1	£16.73	£15.06	£18.40
Trifluridine-tipiracil 20mg / Pack size 60	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil 15mg / Pack size 60	[redacted]	[redacted]	[redacted]
Encorafenib RDI	[redacted]	[redacted]	[redacted]
Cetuximab RDI (initiation)	[redacted]	[redacted]	[redacted]
Cetuximab RDI (maintenance)	[redacted]	[redacted]	[redacted]
Folinic acid RDI	0.72	0.64	0.79
Fluorouracil RDI	0.67	0.61	0.74
Irinotecan RDI	0.73	0.65	0.80
Trifluridine-tipiracil RDI	1.00	0.90	1.10
Chlorphenamine cost	£12.14	£10.93	£13.35
Hydrocortisone cost	£9.09	£8.18	£10.00
Paracetamol cost	£0.11	£0.10	£0.12
Tablet dispensing costs	£15.29	£13.76	£16.82
Vial administration costs	£233.23	£209.91	£256.55
Encorafenib list price	£1,400.00	£1,260.00	£1,540.00
Cetuximab list price (initiation)	£890.50	£801.45	£979.55
Cetuximab list price (maintenance)	£890.50	£801.45	£979.55
Oral chemotherapy day case attendance cost	£163.00	£146.70	£179.30
OC FOLFIRI PF frequency	0.5	0.45	0.55
OC non-FOLFIRI PF frequency	0.5	0.45	0.55
Medical oncologist outpatient consultation cost	£227.00	£204.30	£249.70
MO FOLFIRI PF frequency	0.5	0.45	0.55
MO non-FOLFIRI PF frequency	0.5	0.45	0.55
GP home consultation cost	£100.46	£90.41	£110.51
GP FOLFIRI PD frequency	0.25	0.225	0.275
GP non-FOLFIRI PD frequency	0.25	0.225	0.275
Community nurse specialist cost	£37.00	£33.30	£40.70
CN FOLFIRI PD frequency	1	0.9	1.1
CN non-FOLFIRI PD frequency	1	0.9	1.1
Health home visitor cost	£46.00	£41.40	£50.60
HHV FOLFIRI PF frequency	0.5	0.45	0.55
HHV FOLFIRI PD frequency	1	0.9	1.1
HHV non-FOLFIRI PF frequency	0.5	0.45	0.55
HHV non-FOLFIRI PD frequency	1	0.9	1.1
District nurse cost	£46.00	£41.40	£50.60
DN FOLFIRI PF frequency	4	3.6	4.4

Variable	Base-case value	Low estimate	High estimate
DN FOLFIRI PD frequency	1	0.9	1.1
DN non-FOLFIRI PD frequency	1	0.9	1.1
GP visit cost	£28.16	25.344	30.976
GP FOLFIRI PD frequency	1	0.9	1.1
GP non-FOLFIRI PD frequency	1	0.9	1.1
Terminal care costs	£7,162.14	6445.926	7878.354
Enco with cetuximab trifluridine-tipiracil on progression users	50.00%	0.45	0.55
FOLFIRI trifluridine-tipiracil on progression users	50.00%	0.45	0.55
Irinotecan trifluridine-tipiracil on progression users	50.00%	0.45	0.55
Mean subsequent treatment cycles of trifluridine/tipiracil	2.000	1.8	2.2
Abdominal pain cost	£144.79	£130.31	£159.27
Anaemia cost	£0.00	£0.00	£0.00
Asthenia cost	£163.58	£147.22	£179.94
Cancer pain cost	£144.79	£130.31	£159.27
Decreased appetite cost	£0.00	£0.00	£0.00
Diarrhoea cost	£163.58	£147.22	£179.94
Fatigue cost	£163.58	£147.22	£179.94
Febrile neutropenia cost	£2,806.66	£2,525.99	£3,087.33
Hypertension cost	£879.97	£791.97	£967.97
Intestinal obstruction cost	£215.95	£194.36	£237.55
Leukopenia cost	£2,504.27	£2,253.84	£2,754.70
Liver injury / failure cost	£2,887.00	£2,598.30	£3,175.70
Nausea cost	£0.00	£0.00	£0.00
Neutropenia cost	£2,504.27	£2,253.84	£2,754.70
Stomatitis cost	£163.58	£147.22	£179.94
Thrombocytopenia cost	£640.09	£576.08	£704.10
Urinary tract infection cost	£215.95	£194.36	£237.55
Venous thrombosis cost	£215.95	£194.36	£237.55
Vomiting cost	£163.58	£147.22	£179.94
Abdominal pain rate, Enco with cetuximab	3.24%	2.92%	3.56%
Anaemia rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Asthenia rate, Enco with cetuximab	3.70%	3.33%	4.07%
Cancer pain rate, Enco with cetuximab	2.31%	2.08%	2.55%
Decreased appetite rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Diarrhoea rate, Enco with cetuximab	2.78%	2.50%	3.06%
Fatigue rate, Enco with cetuximab	4.17%	3.75%	4.58%
Febrile neutropenia rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]

Variable	Base-case value	Low estimate	High estimate
Hypertension rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Intestinal obstruction rate, Enco with cetuximab	4.63%	4.17%	5.09%
Leukopenia rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Liver injury / failure rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Nausea rate, Enco with cetuximab	0.00%	0.00%	0.00%
Neutropenia rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Stomatitis rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Thrombocytopenia rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Urinary tract infection rate, Enco with cetuximab	2.31%	2.08%	2.55%
Venous thrombosis rate, Enco with cetuximab	[redacted]	[redacted]	[redacted]
Vomiting rate, Enco with cetuximab	1.39%	1.25%	1.53%
Abdominal pain rate, FOLFIRI	3.60%	3.24%	3.96%
Anaemia rate, FOLFIRI	3.60%	3.24%	3.96%
Asthenia rate, FOLFIRI	0.00%	0.00%	0.00%
Cancer pain rate, FOLFIRI	0.00%	0.00%	0.00%
Decreased appetite rate, FOLFIRI	1.89%	1.70%	2.08%
Diarrhoea rate, FOLFIRI	9.66%	8.69%	10.63%
Fatigue rate, FOLFIRI	7.77%	6.99%	8.54%
Febrile neutropenia rate, FOLFIRI	2.46%	2.22%	2.71%
Hypertension rate, FOLFIRI	2.84%	2.56%	3.13%
Intestinal obstruction rate, FOLFIRI	0.00%	0.00%	0.00%
Leukopenia rate, FOLFIRI	2.65%	2.39%	2.92%
Liver injury / failure rate, FOLFIRI	3.98%	3.58%	4.38%
Nausea rate, FOLFIRI	2.65%	2.39%	2.92%
Neutropenia rate, FOLFIRI	23.30%	20.97%	25.63%
Stomatitis rate, FOLFIRI	2.27%	2.05%	2.50%
Thrombocytopenia rate, FOLFIRI	0.76%	0.68%	0.83%
Urinary tract infection rate, FOLFIRI	0.00%	0.00%	0.00%
Venous thrombosis rate, FOLFIRI	2.08%	1.88%	2.29%
Vomiting rate, FOLFIRI	2.46%	2.22%	2.71%
Abdominal pain rate, Trifluridine-tipiracil	2.44%	2.20%	2.68%
Anaemia rate, Trifluridine-tipiracil	18.18%	16.36%	20.00%
Asthenia rate, Trifluridine-tipiracil	3.38%	3.04%	3.71%
Cancer pain rate, Trifluridine-tipiracil	0.00%	0.00%	0.00%
Decreased appetite rate, Trifluridine-tipiracil	3.56%	3.21%	3.92%
Diarrhoea rate, Trifluridine-tipiracil	3.00%	2.70%	3.30%
Fatigue rate, Trifluridine-tipiracil	3.94%	3.55%	4.33%

Variable	Base-case value	Low estimate	High estimate
Febrile neutropenia rate, Trifluridine-tipiracil	3.75%	3.38%	4.13%
Hypertension rate, Trifluridine-tipiracil	0.00%	0.00%	0.00%
Intestinal obstruction rate, Trifluridine-tipiracil	0.00%	0.00%	0.00%
Leukopenia rate, Trifluridine-tipiracil	21.40%	19.26%	23.54%
Liver injury / failure rate, Trifluridine-tipiracil	0.00%	0.00%	0.00%
Nausea rate, Trifluridine-tipiracil	0.00%	0.00%	0.00%
Neutropenia rate, Trifluridine-tipiracil	37.88%	34.09%	41.67%
Stomatitis rate, Trifluridine-tipiracil	0.00%	0.00%	0.00%
Thrombocytopenia rate, Trifluridine-tipiracil	5.11%	4.60%	5.63%
Urinary tract infection rate, Trifluridine-tipiracil	0.00%	0.00%	0.00%
Venous thrombosis rate, Trifluridine-tipiracil	0.00%	0.00%	0.00%
Vomiting rate, Trifluridine-tipiracil	2.06%	1.86%	2.27%

Abbreviations: BSA, body surface area; CN, community nurse; DN, district nurse; FOLFIRI, folinic acid, fluorouracil, irinotecan; GP, general practitioner; HHV, health home visitor; HR, hazard ratio; OC, oral chemotherapy; OS, overall survival; PD, progressed disease; PF, progression-free; RDI, relative dose intensity.

The pairwise DSA result tornado diagrams are shown in Figure 22 and Figure 23.

Figure 22: DSA results for Enco with cetuximab versus FOLFIRI

Abbreviations: BSA, body surface area; DSA, deterministic sensitivity analysis; E+C, encorafenib with cetuximab; FOLFIRI, folinic acid, fluorouracil, irinotecan; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PPS, post-progression state; RDI, relative dose intensity.

Figure 23: DSA results for Enco with cetuximab versus trifluridine-tipiracil

Abbreviations: BSA, body surface area; DSA, deterministic sensitivity analysis; E+C, encorafenib with cetuximab; FOLFIRI, folinic acid, fluorouracil, irinotecan; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PPS, post-progression state; RDI, relative dose intensity.

B.3.8.3 Summary of PSA and DSA results

The sensitivity analyses show that the model is most sensitive to parameters relating to the costs and utilities associated with Enco with cetuximab and the costs of comparators. This is as expected in a model where the intervention is efficacious, and the comparators are low-cost.

B.3.8.4 Scenario analysis

A summary of the scenario analyses which have been run are described below:

1. Use of Weibull parametric models for survival curves.
2. Use of BEACON CRC control arm as a proxy for FOLFIRI effectiveness.
3. Use of FOLFIRI ITC data as a proxy for trifluridine-tipiracil effectiveness.
4. Use of alternative BRAF-mutant versus BRAF wild-type HRs to estimate trifluridine-tipiracil effectiveness.
5. Use of trifluridine-tipiracil specific utilities.
6. Use of 5-year time horizon.

The first two analyses were selected as potentially plausible, but extreme scenarios. Scenarios 3 and 4 provide alternative estimates of trifluridine-tipiracil effectiveness. Scenario 5 is used as an alternate utility source to the BEACON CRC study, given that trifluridine-tipiracil was not included as a comparator arm in that trial. The sixth scenario was selected to demonstrate the impact of reducing the time horizon assuming that no patients survive beyond five years.

B.3.8.4.1 Scenario 1, Use of Weibull parametric models for survival curves

The use of the Weibull parametric distributions to inform the efficacy of the treatments in the model decreases the cost-effectiveness of Enco with cetuximab primarily due to a decrease in the QALYs gained by patients treated with Enco with cetuximab. The results are shown in Table 67.

Table 67: Scenario 1 deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FOLFIRI	£12,128	0.59	0.40					
Trifluridine-tipiracil	[redacted]	0.37	0.25	[redacted]	-0.21	-0.15	Dominated	Dominated
Enco with cetuximab	[redacted]	1.11	0.76	[redacted]	0.52	0.35	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8.4.2 Scenario 2, Use of BEACON CRC control arm as a proxy for FOLFIRI effectiveness

The efficacy data from BEACON (rather than the ITC) was used in this scenario. As in the base-case, loglogistic parametric models were used for all treatments. The results are shown in Table 68.

Table 68: Scenario 2 deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FOLFIRI	£13,337	0.96	0.64					
Trifluridine-tipiracil	[redacted]	0.38	0.26	[redacted]	-0.59	-0.38	Dominated	Dominated
Enco with cetuximab	[redacted]	1.36	0.92	[redacted]	0.40	0.28	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8.4.3 Scenario 3, Use of FOLFIRI ITC data as a proxy for trifluridine-tipiracil effectiveness

Trifluridine-tipiracil was assumed to be as effective as FOLFIRI in this scenario; the OS and PFS curves for trifluridine-tipiracil were set to be equal to those of FOLFIRI (based on the ITC). This scenario is intended to provide an extreme upper estimate of the potential efficacy of trifluridine-tipiracil in the BRAF V600E population. Clinical experts have advised that trifluridine-tipiracil patients would be expected to have worse outcomes than FOLFIRI patients. The results of this analysis are shown in Table 69.

Table 69: Scenario 3 deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FOLFIRI	£12,204	0.59	0.40					
Trifluridine-tipiracil	[redacted]	0.59	0.40	[redacted]	0.00	0.00	Dominated	Dominated
Enco with cetuximab	[redacted]	1.36	0.92	[redacted]	0.78	0.52	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8.4.4 Scenario 4, Use of alternative BRAF-mutant versus BRAF wild-type HRs to estimate trifluridine-tipiracil effectiveness

A 2012 meta-analysis investigated the differences in OS for BRAF V600E patients versus BRAF wild-type patients (27). The log HR for OS BRAF V600E patients versus BRAF wild-type is presented in Table 70.

Table 70: Alternative log HR for OS in BRAF V600E patients versus BRAF wild-type patients from Safaee Ardekani 2012

Log HR for OS	HR conversion	Source
0.81	2.24	Safaee Ardekani 2012 (27)

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; HR, hazard ratio; OS, overall survival.

As only the log HR for OS was presented, it was assumed that the log HR for PFS would be equivalent to the log HR for OS; a HR of 2.24 was applied to both the OS and PFS curves for trifluridine-tipiracil. The results of this analysis are shown in Table 71.

Table 71: Scenario 4 deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FOLFIRI	£12,204	0.59	0.40					
Trifluridine-tipiracil	[redacted]	0.51	0.35	[redacted]	-0.08	-0.06	Dominated	Dominated
Enco with cetuximab	[redacted]	1.36	0.92	[redacted]	0.78	0.52	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8.4.5 Scenario 5, Use of trifluridine-tipiracil specific utilities

The HSUV SLR (Section B.3.4.3) identified a study which reported UK-specific HSUVs for patients on trifluridine-tipiracil, based on EQ-5D-3L with UK utility tariff applied (108). These utilities were used in the following scenario analysis to assess the possibility that treatment arm is a driver of utility along with progression status. The utility values used for trifluridine-tipiracil are shown in Table 72. The results are shown in Table 73.

Table 72: Utility values for trifluridine-tipiracil patients as obtained from Sabater 2019

Health state	Mean value	Source
Pre-progression utility	0.72	Sabater 2019 (108)
Post-progression utility	0.59	

Table 73: Scenario 5 deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FOLFIRI	£12,204	0.59	0.40					
Trifluridine-tipiracil	[redacted]	0.38	0.25	[redacted]	-0.21	-0.15	Dominated	Dominated
Enco with cetuximab	[redacted]	1.36	0.92	[redacted]	0.78	0.52	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8.4.6 Scenario 6, Use of 5-year time horizon

The results using the 5-year time horizon are shown in Table 74. This scenario assumes that there is no long-term (i.e. beyond 5 years) survival in any of the trial arms.

Table 74: Scenario 6 deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FOLFIRI	£12,201	0.59	0.40					
Trifluridine-tipiracil	[redacted]	0.38	0.26	[redacted]	-0.21	-0.14	Dominated	Dominated
Enco with cetuximab	[redacted]	1.26	0.86	[redacted]	0.68	0.46	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.9 Subgroup analysis

No subgroup analyses were performed.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Internal validation was performed by two senior health economists working independently. Validation consisted of the following:

- A check of all engine calculations.
- Comparing expected values versus generated values when extreme values were entered into the model.
- General logic checks in terms of form controls.
- A check of the PSA and DSA including distributions used and rationales used for distribution choices.
- Independent checking of the IPD and R code used to generate parameters for distributions.
- Validating all values entered into the model against their original sources.

B.3.11 Interpretation and conclusions of economic evidence

The de novo economic evaluation has attempted to estimate the cost-effectiveness of Enco with cetuximab for adult patients with previously treated BRAF V600E-mutant mCRC, in line with its anticipated marketing authorisation and in line with the population in the NICE scope and company decision problem.

The analysis provides comparisons with comparators which are deemed to be of relevance to clinical practice in the UK in this post first-line setting, namely FOLFIRI and trifluridine-tipiracil. As described in Table 1, single-agent irinotecan and BSC are not

considered to be relevant comparators for clinical practice in England, and hence analyses including these comparators were not provided.

When interpreting any of the analyses provided it should be recognised that all results are based on cetuximab list price and do not take account of the confidential commercial discount that would be applicable to combination treatment with Enco in the mCRC setting. As such, the results are not representative of the true cost-effectiveness estimates anticipated for Enco with cetuximab.

In the BRAF-mutant population for which clinical evidence for comparators is extremely limited, the analysis has made use of the best available evidence identified by systematic means. For Enco with cetuximab, effectiveness, safety and EQ-5D data was derived from the Phase 3 RCT, BEACON CRC, which was specifically designed to investigate the effectiveness and safety of the encorafenib regimen in the BRAF-mutant population, and hence represents the most robust evidence available. For FOLFIRI, only limited evidence was available from BRAF-mutant subgroups within RCTs and assumptions had to be made with regard to equivalence of some therapies (e.g. assuming that cetuximab and panitumumab were equivalent) to enable a “grouped treatment nodes” ITC. In this way Enco with cetuximab and FOLFIRI could be compared to enable cost-effectiveness analyses. As described previously (Section B.2.14.2.2.4), although the BEACON control arm did include FOLFIRI, this was in combination with cetuximab, and the relative benefit of cetuximab within that control arm is unknown. As such, using the BEACON CRC control arm as a proxy for FOLFIRI effectiveness would overestimate the effect of FOLFIRI when taken without cetuximab and therefore underestimate the additional benefit seen with the encorafenib regimen. Accordingly, Pierre Fabre believe the ITC to be the most robust estimate of relative effectiveness for use as a base-case economic analysis.

For trifluridine-tipiracil no data was identified in a BRAF-mutant population, and an ITC was therefore not feasible. A naïve comparison had to be undertaken, utilising K-M curves from an RCT in which the population comprised ~50% KRAS wild-type, K50% RAS-mutant, with no assessment of BRAF status reported. Since BRAF-mutations are known to confer poorer outcomes on patients than BRAF wild-type, K-M curves had to be adjusted using HRs for OS and PFS for BRAF wild-type versus BRAF-mutant. Given the use of naïve comparison and the need to adjust for BRAF-mutations it is recognised that economic analyses versus trifluridine-tipiracil will be subject to greater uncertainty; additional scenarios have been provided to try to account for alternate estimates of

trifluridine-tipiracil effectiveness (Section B.3.8.4), but holding all other base-case assumptions unchanged, varying effectiveness estimates of trifluridine-tipiracil generates the same overall conclusion that trifluridine-tipiracil is dominated by FOLFIRI.

In terms of survival curves loglogistic was deemed to be most appropriate for base-case analyses (See Section B.3.3.1.1.4). The loglogistic model predicted approximately 4% of patients in the Enco with cetuximab arm and 2.4% of patients in the control arm of BEACON were still alive at 60 months. Data from Cancer Research UK suggests that 10.3% of all patients with mCRC would be alive after 60 months (22). Even after adjusting this survival rate for the poorer prognosis observed with BRAF-mutations (Published HRs for BRAF-mutant vs BRAF wild-type OS: HR 2.24 from Safaee Ardekani meta-analysis of RCTs and cohort studies (27); HR 4.0 from Peeters 2015 (42)) it might be expected that a small proportion of patients on current treatments would still be alive at the 60 month timepoint. The Weibull models predicted that almost all patients (>99%) had died at 60 months across all treatment arms. This scenario will be a more conservative estimation of effectiveness in that it may be overly pessimistic. When modelling Weibull the incremental ICERs increase from £[redacted] to £[redacted], driven by a reduction in the QALY gain for the encorafenib regimen vs FOLFIRI. This is not unsurprising given that almost all patients have died by 60 months in the Weibull model compared with 4% alive in the loglogistic model.

All costs are taken from UK cost sources, including eMIT, BNF, NHS Reference costs and previous NICE TAs.

The economic analyses reported here provide estimates of cost-effectiveness for Enco with cetuximab versus the comparators of relevance to clinical practice in the UK in this post first-line setting, namely FOLFIRI and trifluridine-tipiracil. The true cost-effectiveness will need to be re-assessed using the confidential discount price which is available for cetuximab in this indication.

A positive NICE recommendation for Enco with cetuximab will provide patients and clinicians with a first-in-class oral and chemotherapy-free targeted therapy for BRAF V600E-mutant mCRC patients who have received prior systemic therapy for which there is a clear and substantial unmet need.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions
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Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: BEACON CRC study, additional information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Encorafenib in dual therapy with cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Clarification questions

Pierre Fabre responses

March 2020

File name	*Version*	*Contains confidential information*	*Date*
ID1598 encorafenib ERG clarification questions v1.0 to PM [ACIC].docx	*1*	*Yes*	*25 March 2020*

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Queries and additional data required for evaluating clinical effectiveness

A1. Priority question: Please present Company Submission (CS) Document B, Table 4, BEACON baseline characteristics, with the control arm split into two columns: (1) FOLFIRI+cetuximab patients, and (2) irinotecan+cetuximab patients. Please also present this data for the subset of European patients and for the subset of 1 prior mCRC therapy.

Analyses are provided for the overall trial population (Table 1), 1 prior mCRC therapy (Table 2) and European patients (Table 3).

Table 1: Baseline characteristics and demographics (FAS)

	Enco with cetuximab (N=220)	***Control (N=221)***	***FOLFIRI with cetuximab (N=129)***	***Irinotecan with cetuximab (N=92)***
Sex- n(%)				
Female	*106 (48.2)[a]*	*127 (57.5)*	[redacted]	[redacted]
Male	*114 (51.8)*	*94 (42.5)*	[redacted]	[redacted]
Age				
n	*220*	*221*	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	*61.0*	*60.0*	[redacted]	[redacted]
Min; Max	*30; 91*	*27; 91*	[redacted]	[redacted]
Race (N)- n(%)				
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Not reported due to confidentiality reason	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS at Baseline- n(%)				
0	*112 (50.9)*	*108 (48.9)*	[redacted]	[redacted]
1	*104 (47.3)*	*113 (51.1)*	[redacted]	[redacted]
2	*4 (1.8)*	*0 (0.0)*	[redacted]	[redacted]
Number of Prior Systemic Regimens- n(%)				
1	*146 (66.4)*	*145 (65.6)*	[redacted]	[redacted]

	Enco with cetuximab (N=220)	Control (N=221)	FOLFIRI with cetuximab (N=129)	Irinotecan with cetuximab (N=92)
2	74 (33.6)	75 (33.9)	[redacted]	[redacted]
3	0 (0.0)	1 (0.5)	[redacted]	[redacted]
Prior Use of Irinotecan- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Prior Use of Oxaliplatin (N)- n(%)				
Y	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Location of Primary Tumor (N)- n(%)				
Left Colon	83 (37.7)	68 (30.8)	[redacted]	[redacted]
Right Colon	110 (50.0)	119 (53.8)	[redacted]	[redacted]
Both Sides	[redacted]	[redacted]	[redacted]	[redacted]
Unknown Colon	[redacted]	[redacted]	[redacted]	[redacted]
Primary tumour removed- n(%)				
Completely resected	123 (55.9)	122 (55.2)	[redacted]	[redacted]
Partially Resected/Unresected	97 (44.1)	99 (44.8)	[redacted]	[redacted]
Number of Involved Organs at Baseline				
n	220	221	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
N Organs at Baseline- n(%)				
<=2	117 (53.2)	123 (55.7)	[redacted]	[redacted]
3+	103 (46.8)	98 (44.3)	[redacted]	[redacted]
Liver Mets at Baseline- n(%)				
N	86 (39.1)	93 (42.1)	[redacted]	[redacted]
Y	134 (60.9)	128 (57.9)	[redacted]	[redacted]
Lung Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Lymph Node Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]

	Enco with cetuximab (N=220)	Control (N=221)	FOLFIRI with cetuximab (N=129)	Irinotecan with cetuximab (N=92)
Peritoneum/Omentum Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
MSI Status (PCR) at Baseline (N)- n(%)				
Abnormal High	19 (8.6)	12 (5.4)	[redacted]	[redacted]
Normal	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal Low	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
CEA NR Indicator at Baseline (N)- n(%)				
>ULN	153 (69.5)	178 (80.5)	[redacted]	[redacted]
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
CRP NR Indicator at Baseline (N)- n(%)				
>ULN	79 (35.9)	90 (40.7)	[redacted]	[redacted]
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAS, Full Analysis Set; MSI, microsatellite instability; PCR, polymerase chain reaction; SD, standard deviation; ULN, upper limit of normal.

[a] For August 2019 dataset, Sex for 1 patient in the Doublet arm was recategorized from "male" to "female".

Table 2: Baseline characteristics and demographics (FAS - 1 prior mCRC therapy])

	Enco with cetuximab (N=146)	Control (N=145)	FOLFIRI with cetuximab (N=95)	Irinotecan with cetuximab (N=50)
Sex- n(%)				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]
Age				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Race (N)- n(%)				
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]

	Enco with cetuximab (N=146)	Control (N=145)	FOLFIRI with cetuximab (N=95)	Irinotecan with cetuximab (N=50)
White	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Not reported due to confidentiality reason	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS at Baseline- n(%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
Number of Prior Systemic Regimens- n(%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
Prior Use of Irinotecan- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Prior Use of Oxaliplatin (N)- n(%)				
Y	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Location of Primary Tumor (N)- n(%)				
Left Colon	[redacted]	[redacted]	[redacted]	[redacted]
Right Colon	[redacted]	[redacted]	[redacted]	[redacted]
Both Sides	[redacted]	[redacted]	[redacted]	[redacted]
Unknown Colon	[redacted]	[redacted]	[redacted]	[redacted]
Primary tumour removed- n(%)				
Completely resected	[redacted]	[redacted]	[redacted]	[redacted]
Partially Resected/Unresected	[redacted]	[redacted]	[redacted]	[redacted]
Number of Involved Organs at Baseline				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
N Organs at Baseline- n(%)				
<=2	[redacted]	[redacted]	[redacted]	[redacted]
3+	[redacted]	[redacted]	[redacted]	[redacted]
Liver Mets at Baseline- n(%)				

	Enco with cetuximab (N=146)	Control (N=145)	FOLFIRI with cetuximab (N=95)	Irinotecan with cetuximab (N=50)
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Lung Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Lymph Node Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Peritoneum/Omentum Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
MSI Status (PCR) at Baseline (N)- n(%)				
Abnormal High	[redacted]	[redacted]	[redacted]	[redacted]
Normal	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal Low	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
CEA NR Indicator at Baseline (N)- n(%)				
>ULN	[redacted]	[redacted]	[redacted]	[redacted]
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
CRP NR Indicator at Baseline (N)- n(%)				
>ULN	[redacted]	[redacted]	[redacted]	[redacted]
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAS, Full Analysis Set; MSI, microsatellite instability; PCR, polymerase chain reaction; SD, standard deviation; ULN, upper limit of normal.

Table 3: Baseline characteristics and demographics (FAS - European patients)

	Enco with cetuximab (N=144)	Control (N=125)	FOLFIRI with cetuximab (N=68)	Irinotecan with cetuximab (N=57)
Sex- n(%)				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]

	Enco with cetuximab (N=144)	Control (N=125)	FOLFIRI with cetuximab (N=68)	Irinotecan with cetuximab (N=57)
Age				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
Race (N)- n(%)				
Asian	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Not reported due to confidentiality reason	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS at Baseline- n(%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
Number of Prior Systemic Regimens- n(%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
Prior Use of Irinotecan- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Prior Use of Oxaliplatin (N)- n(%)				
Y	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Location of Primary Tumor (N)- n(%)				
Left Colon	[redacted]	[redacted]	[redacted]	[redacted]
Right Colon	[redacted]	[redacted]	[redacted]	[redacted]
Both Sides	[redacted]	[redacted]	[redacted]	[redacted]
Unknown Colon	[redacted]	[redacted]	[redacted]	[redacted]
Primary tumour removed- n(%)				
Completely resected	[redacted]	[redacted]	[redacted]	[redacted]
Partially Resected/Unresected	[redacted]	[redacted]	[redacted]	[redacted]
Number of Involved Organs at Baseline				

	Enco with cetuximab (N=144)	Control (N=125)	FOLFIRI with cetuximab (N=68)	Irinotecan with cetuximab (N=57)
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]	[redacted]	[redacted]
N Organs at Baseline- n(%)				
<=2	[redacted]	[redacted]	[redacted]	[redacted]
3+	[redacted]	[redacted]	[redacted]	[redacted]
Liver Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Lung Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Lymph Node Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
Peritoneum/Omentum Mets at Baseline- n(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
MSI Status (PCR) at Baseline (N)- n(%)				
Abnormal High	[redacted]	[redacted]	[redacted]	[redacted]
Normal	[redacted]	[redacted]	[redacted]	[redacted]
Not Evaluable	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal Low	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
CEA NR Indicator at Baseline (N)- n(%)				
>ULN	[redacted]	[redacted]	[redacted]	[redacted]
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]
CRP NR Indicator at Baseline (N)- n(%)				
>ULN	[redacted]	[redacted]	[redacted]	[redacted]
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAS, Full Analysis Set; MSI, microsatellite instability; PCR, polymerase chain reaction; SD, standard deviation; ULN, upper limit of normal.

A2. Priority question: Please present BEACON OS Kaplan Meier Aug 2019 data split by arm, with the control arm split into two subgroups: (1) FOLFIRI+cetuximab baseline patients, and (2) irinotecan+cetuximab baseline patients, in the following format (4 tables). Please also present this data for the subset of 1 prior mCRC therapy (4 tables). If other events need to be added to the mutually exclusive events of the table please do so. Please state which events should be treated as censoring and which as OS events when constructing the KM curves.

OS analyses are provided for the overall trial population (Enco with cetuximab Table 4; control Table 5; control FOLFIRI with cetuximab Table 6; control irinotecan with cetuximab Table 7) and 1 prior mCRC therapy (Enco with cetuximab Table 8; control Table 9; control FOLFIRI with cetuximab Table 10; control irinotecan with cetuximab Table 11).

Table 4: Overall survival - events and subjects censored by timepoint - (FAS – Enco with cetuximab)

		Events			
Timepoint	*N at risk*	*Death*	*Ongoing Without Event **	*Withdrawal of Consent **	*Lost to Follow-up **
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 5: Overall survival - events and subjects censored by timepoint - (FAS – Control)

		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
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		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
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		Events			
Timepoint	*N at risk*	*Death*	*Ongoing Without Event **	*Withdrawal of Consent **	*Lost to Follow-up **
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 6: Overall survival - events and subjects censored by timepoint - (FAS – FOLFIRI with cetuximab)

		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
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		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
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		Events		
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *
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		Events		
Timepoint	**N at risk**	**Death**	**Ongoing Without Event ***	**Withdrawal of Consent ***
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 7: Overall survival - events and subjects censored by timepoint - (FAS – irinotecan with cetuximab)

		Events			
Timepoint	**N at risk**	**Death**	**Ongoing Without Event ***	**Withdrawal of Consent ***	**Lost to Follow-up ***
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		Events			
Timepoint	*N at risk*	*Death*	*Ongoing Without Event **	*Withdrawal of Consent **	*Lost to Follow-up **
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 8: Overall survival - events and subjects censored by timepoint - (FAS – Enco with cetuximab, 1 prior mCRC therapy)

		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
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		Events			
Timepoint	*N at risk*	*Death*	*Ongoing Without Event **	*Withdrawal of Consent **	*Lost to Follow-up **
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
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		Events			
Timepoint	*N at risk*	*Death*	*Ongoing Without Event **	*Withdrawal of Consent **	*Lost to Follow-up **
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		Events			
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****	***Lost to Follow-up ****
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 9: Overall survival - events and subjects censored by timepoint - (FAS – Control, 1 prior mCRC therapy)

		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events		
Timepoint	*N at risk*	*Death*	*Ongoing Without Event **	*Withdrawal of Consent **
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 10: Overall survival - events and subjects censored by timepoint - (FAS – FOLFIRI with cetuximab, 1 prior mCRC therapy)

		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events		
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 11: Overall survival - events and subjects censored by timepoint - (FAS – irinotecan with cetuximab, 1 prior mCRC therapy)

		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events		
Timepoint	***N at risk***	***Death***	***Ongoing Without Event ****	***Withdrawal of Consent ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

A3. Priority question: Please present the BEACON PFS Kaplan Meier Aug 2019 data split by arm, with the control arm split into two subgroups: (1) FOLFIRI+cetuximab baseline patients, and (2) irinotecan+cetuximab baseline patients, in the following format (4 tables). Please also present this data for the subset of 1 prior mCRC therapy (4 tables). If other events need to be added to the mutually exclusive events of the table please do so. Please state which events should be treated as censoring and which as PFS events when constructing the KM curves.

PFS analyses are provided for the overall trial population (Enco with cetuximab Table 12; control Table 13; control FOLFIRI with cetuximab Table 14; control irinotecan with cetuximab Table 15) and 1 prior mCRC therapy (Enco with cetuximab Table 16; control Table 17; control FOLFIRI with cetuximab Table 18; control irinotecan with cetuximab Table 19).

Table 12: PFS - Events and subjects censored by timepoint - (FAS – Enco with cetuximab)

		Events								
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Progression after 2 or more missed assessments ****	***Last adequate assessment ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events								
Timepoint	N at risk	Death	Progression	No baseline assessment *	No adequate post-baseline assessment *	Subsequent therapy given *	Progression after 2 or more missed assessments *	Last adequate assessment *	Withdrawal of consent *	Ongoing tumour assessments *
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		Events								
Timepoint	**N at risk**	**Death**	**Progression**	**No baseline assessment ***	**No adequate post-baseline assessment ***	**Subsequent therapy given ***	**Progression after 2 or more missed assessments ***	**Last adequate assessment ***	**Withdrawal of consent ***	**Ongoing tumour assessments ***
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		Events								
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Progression after 2 or more missed assessments ****	***Last adequate assessment ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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		Events								
Timepoint	**N at risk**	**Death**	**Progression**	**No baseline assessment ***	**No adequate post-baseline assessment ***	**Subsequent therapy given ***	**Progression after 2 or more missed assessments ***	**Last adequate assessment ***	**Withdrawal of consent ***	**Ongoing tumour assessments ***
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		Events								
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Progression after 2 or more missed assessments ****	***Last adequate assessment ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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		Events								
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Progression after 2 or more missed assessments ****	***Last adequate assessment ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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** Reason for censoring.*

Table 13: PFS - Events and subjects censored by timepoint - (FAS – Control)

		Events								
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Death after 2 or more missed assessments ****	***Last adequate assessment ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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		Events								
Timepoint	**N at risk**	**Death**	**Progression**	**No baseline assessment ***	**No adequate post-baseline assessment ***	**Subsequent therapy given ***	**Death after 2 or more missed assessments ***	**Last adequate assessment ***	**Withdrawal of consent ***	**Ongoing tumour assessments ***
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		Events								
Timepoint	**N at risk**	**Death**	**Progression**	**No baseline assessment ***	**No adequate post-baseline assessment ***	**Subsequent therapy given ***	**Death after 2 or more missed assessments ***	**Last adequate assessment ***	**Withdrawal of consent ***	**Ongoing tumour assessments ***
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		Events								
Timepoint	N at risk	Death	Progression	No baseline assessment *	No adequate post-baseline assessment *	Subsequent therapy given *	Death after 2 or more missed assessments *	Last adequate assessment *	Withdrawal of consent *	Ongoing tumour assessments *
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		Events								
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Death after 2 or more missed assessments ****	***Last adequate assessment ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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** Reason for censoring.*

Table 14: PFS - Events and subjects censored by timepoint - (FAS – FOLFIRI with cetuximab)

		Events						
Timepoint	***N at risk***	***Death***	***Progression***	***No Baseline Assessment ****	***Subsequent Therapy Given ****	***Death After 2 or more Missed Assessments ****	***Withdrawal of Consent ****	***Ongoing Tumour Assessments ****
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		Events						
Timepoint	***N at risk***	***Death***	***Progression***	***No Baseline Assessment ****	***Subsequent Therapy Given ****	***Death After 2 or more Missed Assessments ****	***Withdrawal of Consent ****	***Ongoing Tumour Assessments ****
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		Events						
Timepoint	***N at risk***	***Death***	***Progression***	***No Baseline Assessment ****	***Subsequent Therapy Given ****	***Death After 2 or more Missed Assessments ****	***Withdrawal of Consent ****	***Ongoing Tumour Assessments ****
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		Events						
Timepoint	***N at risk***	***Death***	***Progression***	***No Baseline Assessment ****	***Subsequent Therapy Given ****	***Death After 2 or more Missed Assessments ****	***Withdrawal of Consent ****	***Ongoing Tumour Assessments ****
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** Reason for censoring.*

Table 15: PFS - Events and subjects censored by timepoint - (FAS – irinotecan with cetuximab)

		Events								
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Death after 2 or more missed assessments ****	***Last adequate assessment ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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		Events								
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Death after 2 or more missed assessments ****	***Last adequate assessment ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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		Events								
Timepoint	N at risk	Death	Progression	No baseline assessment *	No adequate post-baseline assessment *	Subsequent therapy given *	Death after 2 or more missed assessments *	Last adequate assessment *	Withdrawal of consent *	Ongoing tumour assessments *
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** Reason for censoring.*

Table 16: PFS - Events and subjects censored by timepoint - (FAS – Enco with cetuximab, 1 prior mCRC therapy)

		Events							
Timepoint	N at risk	Death	Progression	No Baseline Assessment *	Subsequent Therapy Given *	Progression After 2 or more Missed Assessments *	Last Adequate Assessment *	Withdrawal of Consent *	Ongoing Tumour Assessments *
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		Events							
Timepoint	***N at risk***	***Death***	***Progression***	***No Baseline Assessment ****	***Subsequent Therapy Given ****	***Progression After 2 or more Missed Assessments ****	***Last Adequate Assessment ****	***Withdrawal of Consent ****	***Ongoing Tumour Assessments ****
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		Events							
Timepoint	***N at risk***	***Death***	***Progression***	***No Baseline Assessment ****	***Subsequent Therapy Given ****	***Progression After 2 or more Missed Assessments ****	***Last Adequate Assessment ****	***Withdrawal of Consent ****	***Ongoing Tumour Assessments ****
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		Events							
Timepoint	***N at risk***	***Death***	***Progression***	***No Baseline Assessment ****	***Subsequent Therapy Given ****	***Progression After 2 or more Missed Assessments ****	***Last Adequate Assessment ****	***Withdrawal of Consent ****	***Ongoing Tumour Assessments ****
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		Events							
Timepoint	**N at risk**	**Death**	**Progression**	**No Baseline Assessment ***	**Subsequent Therapy Given ***	**Progression After 2 or more Missed Assessments ***	**Last Adequate Assessment ***	**Withdrawal of Consent ***	**Ongoing Tumour Assessments ***
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** Reason for censoring.*

Table 17: PFS - Events and subjects censored by timepoint - (FAS – Control, 1 prior mCRC therapy)

		Events							
Timepoint	**N at risk**	**Death**	**Progression**	**No baseline assessment ***	**No adequate post-baseline assessment ***	**Subsequent therapy given ***	**Death after 2 or more missed assessments ***	**Withdrawal of consent ***	**Ongoing tumour assessments ***
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		Events							
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Death after 2 or more missed assessments ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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		Events							
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Death after 2 or more missed assessments ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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		Events							
Timepoint	*N at risk*	*Death*	*Progression*	*No baseline assessment **	*No adequate post-baseline assessment **	*Subsequent therapy given **	*Death after 2 or more missed assessments **	*Withdrawal of consent **	*Ongoing tumour assessments **
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** Reason for censoring.*

Table 18: PFS - Events and subjects censored by timepoint - (FAS – FOLFIRI with cetuximab, 1 prior mCRC therapy)

		Events						
Timepoint	*N at risk*	*Death*	*Progression*	*No baseline assessment **	*Subsequent therapy given **	*Death after 2 or more missed assessments **	*Withdrawal of consent **	*Ongoing tumour assessments **
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		Events						
Timepoint	***N at risk***	***Death***	***Progression***	***No baseline assessment ****	***Subsequent therapy given ****	***Death after 2 or more missed assessments ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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		Events						
Timepoint	N at risk	Death	Progression	No baseline assessment *	Subsequent therapy given *	Death after 2 or more missed assessments *	Withdrawal of consent *	Ongoing tumour assessments *
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		Events						
Timepoint	**N at risk**	**Death**	**Progression**	**No baseline assessment ***	**Subsequent therapy given ***	**Death after 2 or more missed assessments ***	**Withdrawal of consent ***	**Ongoing tumour assessments ***
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** Reason for censoring.*

Table 19: PFS - Events and subjects censored by timepoint - (FAS – irinotecan with cetuximab, 1 prior mCRC therapy)

		Events						
Timepoint	**N at risk**	**Death**	**Progression**	**No adequate post-baseline assessment ***	**Subsequent therapy given ***	**Death after 2 or more missed assessments ***	**Withdrawal of consent ***	**Ongoing tumour assessments ***
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		Events						
Timepoint	**N at risk**	**Death**	**Progression**	**No adequate post-baseline assessment ***	**Subsequent therapy given ***	**Death after 2 or more missed assessments ***	**Withdrawal of consent ***	**Ongoing tumour assessments ***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events						
Timepoint	***N at risk***	***Death***	***Progression***	***No adequate post-baseline assessment ****	***Subsequent therapy given ****	***Death after 2 or more missed assessments ****	***Withdrawal of consent ****	***Ongoing tumour assessments ****
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** Reason for censoring.*

A4. Priority question: Please present the BEACON post-progression survival Kaplan Meier Aug 2019 data split by arm treating the date of the first assessment of the patient having progressed as Day=0, with the control arm split into two subgroups: (1) FOLFIRI+cetuximab baseline patients, and (2) irinotecan+cetuximab baseline patients, in the following format (4 tables). Please also present this data for the subset of 1 prior mCRC therapy (4 tables). If other events need to be added to the mutually exclusive events of the table please do so. Please state which events should be treated as censoring and which as PPS OS events when constructing the KM curves.

Post-progression survival analyses are provided for the overall trial population (Enco with cetuximab Table 20; control Table 21; control FOLFIRI with cetuximab Table 22; control irinotecan with cetuximab Table 23) and 1 prior mCRC therapy (Enco with cetuximab Table 24; control Table 25; control FOLFIRI with cetuximab Table 26; control irinotecan with cetuximab Table 27).

Table 20: PPS - Events and subjects censored by timepoint - (FAS – Enco with cetuximab)

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
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Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
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Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
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Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
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Timepoint	***N at risk***	***Death***	***Ongoing without event****	***Withdrawal of consent****	***Lost to follow-up****
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Timepoint	***N at risk***	***Death***	***Ongoing without event****	***Withdrawal of consent****	***Lost to follow-up****
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Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
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** Reason for censoring.*

Table 21: PPS - Events and subjects censored by timepoint - (FAS – Control)

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
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Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
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Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	***N at risk***	***Death***	***Ongoing without event****	***Withdrawal of consent****	***Lost to follow-up****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 22: PPS - Events and subjects censored by timepoint - (FAS – FOLFIRI with cetuximab)

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 23: PPS - Events and subjects censored by timepoint - (FAS – irinotecan with cetuximab)

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 24: PPS - Events and subjects censored by timepoint - (FAS – Enco with cetuximab, 1 prior mCRC therapy)

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	***N at risk***	***Death***	***Ongoing without event****	***Withdrawal of consent****	***Lost to follow-up****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 25: PPS - Events and subjects censored by timepoint - (FAS – Control, 1 prior mCRC therapy)

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	***N at risk***	***Death***	***Ongoing without event****	***Withdrawal of consent****	***Lost to follow-up****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 26: PPS - Events and subjects censored by timepoint - (FAS – FOLFIRI with cetuximab, 1 prior mCRC therapy)

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

Table 27: PPS - Events and subjects censored by timepoint - (FAS – irinotecan with cetuximab, 1 prior mCRC therapy)

Timepoint	N at risk	Death	Ongoing without event*	Withdrawal of consent*	Lost to follow-up*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Timepoint	*N at risk*	*Death*	*Ongoing without event**	*Withdrawal of consent**	*Lost to follow-up**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

A5. Priority question: Please present the BEACON TTD Kaplan Meier Aug 2019 data split by arm, with the control arm split into two subgroups: (1) FOLFIRI+cetuximab baseline patients, and (2) irinotecan+cetuximab baseline patients, in the following format (4 tables). Please also present this data for the subset of 1 prior mCRC therapy (4 tables). If other events need to be added to the mutually exclusive events of the table please do so. Please state which events should be treated as censoring and which as treatment discontinuation events when constructing the KM curves.

TTD analyses are provided for the overall trial population (Enco with cetuximab Table 28; control Table 29; control FOLFIRI with cetuximab Table 30; control irinotecan with cetuximab Table 31) and 1 prior mCRC therapy (Enco with cetuximab Table 32; control Table 33; control FOLFIRI with cetuximab Table 34; control irinotecan with cetuximab Table 35).

Table 28: TTD - Events and subjects censored by timepoint - (Safety set – Enco with cetuximab)

		Events					
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Cutoff ****	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events					
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Cutoff ****	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Cutoff ****	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
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		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
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** Reason for censoring.*

Table 29: TTD - Events and subjects censored by timepoint - (Safety set – Control)

		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
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** Reason for censoring.*

Table 30: TTD - Events and subjects censored by timepoint - (Safety set – FOLFIRI with cetuximab)

		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events					
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Cutoff ****	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 31: TTD - Events and subjects censored by timepoint - (Safety set – irinotecan with cetuximab)

		Events					
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Cutoff ****	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 32: TTD - Events and subjects censored by timepoint - (Safety set – Enco with cetuximab, 1 prior mCRC therapy)

		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	N at risk	Discontinuation (All Trt)	Cutoff *	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
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		Events					
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Cutoff ***	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
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		Events					
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Cutoff ****	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 33: TTD - Events and subjects censored by timepoint - (Safety set – Control, 1 prior mCRC therapy)

		Events				
Timepoint	*N at risk*	*Discontinuation (All Trt)*	*Death **	*Last Contact **	*Subsequent Therapy **	*Treatment End + 30 **
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		Events				
Timepoint	*N at risk*	*Discontinuation (All Trt)*	*Death **	*Last Contact **	*Subsequent Therapy **	*Treatment End + 30 **
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events				
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
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		Events				
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 34: TTD - Events and subjects censored by timepoint - (Safety set – FOLFIRI with cetuximab, 1 prior mCRC therapy)

		Events				
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events				
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events				
Timepoint	**N at risk**	**Discontinuation (All Trt)**	**Death ***	**Last Contact ***	**Subsequent Therapy ***	**Treatment End + 30 ***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events				
Timepoint	*N at risk*	*Discontinuation (All Trt)*	*Death **	*Last Contact **	*Subsequent Therapy **	*Treatment End + 30 **
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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** Reason for censoring.*

Table 35: TTD - events and subjects censored by timepoint - (Safety set – irinotecan with cetuximab, 1 prior mCRC therapy)

		Events				
Timepoint	*N at risk*	*Discontinuation (All Trt)*	*Death **	*Last Contact **	*Subsequent Therapy **	*Treatment End + 30 **
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events				
Timepoint	N at risk	Discontinuation (All Trt)	Death *	Last Contact *	Subsequent Therapy *	Treatment End + 30 *
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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		Events				
Timepoint	***N at risk***	***Discontinuation (All Trt)***	***Death ****	***Last Contact ****	***Subsequent Therapy ****	***Treatment End + 30 ****
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Reason for censoring.*

A6. For patients who were randomised, but did not receive any dose of allocated treatment in the BEACON trial (see CS Document B Appendices, Page 111, Figure 3), please clarify: (1) whether they were followed up for effectiveness and safety measures; (2) if they were not subsequently followed up, whether their data were included in the analyses of the Full Analysis Set (FAS) and the Phase 3 Response Efficacy Set, for OS, ORR, PFS, DOR, TTR and patient reported quality of life measures; and (3) if they were included in the analyses, whether their data were censored or any imputation methods were used.

[redacted]

SAFFL	PARAMCD	PARAM	CNSR	EVNTDESC	Frequency
N	TTDEQVAS	EQ-5D-5L EQ5D5L06 Time to Deterioration (months)	0	Death	22
N	TTDEQVAS	EQ-5D-5L EQ5D5L06 Time to Deterioration (months)	1	No Definitive Deterioration	12

SAFFL	PARAMCD	PARAM	CNSR	EVNTDESC	Frequency
N	TTDEOQOL	EORTC QLQ-C30 QOL Time to Deterioration (months)	0	Death	22
N	TTDEOQOL	EORTC QLQ-C30 QOL Time to Deterioration (months)	1	No Definitive Deterioration	12

SAFFL	PARAMCD	PARAM	CNSR	EVNTDESC	Frequency
N	TTDFAFWB	FACT-C FWB Time to Deterioration (months)	0	Death	22
N	TTDFAFWB	FACT-C FWB Time to Deterioration (months)	1	No Definitive Deterioration	12

A7. In the BEACON control arm what proportion of FOLFIRI+cetuximab baseline patients subsequently went on to receive irinotecan (±cetuximab) during (1) PFS and (2) post-progression? Similarly, in the BEACON control arm what proportion of irinotecan+cetuximab baseline patients subsequently went on to receive FOLFIRI (±cetuximab) during (1) PFS and (2) post-progression?

As shown in Table 36 and Table 37, few patients went on to receive irinotecan with cetuximab after being treated with FOLFIRI with cetuximab, or FOLFIRI with cetuximab after being treated with irinotecan with cetuximab. We find these numbers consistent as it is unusual to switch therapies which are in the same therapeutic area.

- *[redacted] patients who received FOLFIRI with cetuximab at baseline subsequently went on to receive irinotecan with cetuximab (Table 36).*

Table 36: FOLFIRI with cetuximab baseline patients who subsequently went on to receive irinotecan with cetuximab during (1) PFS and (2) post-progression

FOLFIRI with cetuximab -> irinotecan with cetuximab	*Number of patients*
During PFS (before event)	[redacted]
During PPS (after event)	[redacted]

Abbreviations: PFS, progression-free survival; PS, post-progression survival.

- *[redacted] patient who received irinotecan with cetuximab at baseline subsequently went on to receive FOLFIRI with cetuximab (Table 37).*

Table 37: Irinotecan with cetuximab baseline patients who subsequently went on to receive FOLFIRI with cetuximab during (1) PFS and (2) post-progression

Irinotecan with cetuximab -> FOLFIRI with cetuximab	*Number of patients*
During PFS (before event)	[redacted]
During PPS (after event)	[redacted]

Abbreviations: PFS, progression-free survival; PS, post-progression survival.

A8. With regard to CS Document B, Section B.2.4.11, Table 4, please tabulate the range of prior mCRC therapies, N patients for each, by arm for the subgroup with only 1 prior therapy, with the control arm split into two columns: (1) FOLFIRI+cetuximab patients, and (2) irinotecan+cetuximab patients. Please also present this data for the subgroup with ≥2 prior therapies.

Relevant data is provided in Table 38 for 1 prior therapy and in Table 39 for ≥2 prior therapies.

Table 38: Prior therapy used by line of treatment and control arm split (FAS - 1 prior mCRC therapy)

	FOLFIRI with cetuximab (N=95)	***Irinotecan with cetuximab (N=50)***
Prior therapy used - n(%)		
Irinotecan	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]

Table 39: Prior therapy used by line of treatment and control arm split (FAS - ≥2 prior mCRC therapy)

	FOLFIRI with cetuximab (N=34)	***Irinotecan with cetuximab (N=42)***
Prior therapy used - n(%)		
Irinotecan	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]

A9. CS Document B, Sections B.2.7.1, B.2.7.2 and B.2.7.3, supportive analyses: for multivariate Cox regression for OS, ORR and PFS, please provide the adjusted hazard ratios for all co-variates included in the models and the number of patients included in each analysis:

Table 40: Stratified multivariate cox regression model for OS Enco with cetuximab vs control, FAS (n numbers not available)

	Hazard ratio	***95% CI***	***p-value (2-sided)***
Full cox regression model			
Enco with cetuximab vs. control	[redacted]	[redacted]	[redacted]
Covariates			
Gender (male vs. Female)	[redacted]	[redacted]	[redacted]
Age (<65 vs. >=65 years)	[redacted]	[redacted]	[redacted]
Removal of primary tumour (Complete resection vs. Partial resection/unresected)	[redacted]	[redacted]	[redacted]
Baseline CRP (<=ULN vs. >ULN)	[redacted]	[redacted]	[redacted]
Side of tumour			[redacted]
Left colon vs. Right colon	[redacted]	[redacted]	[redacted]
Left/right colon vs. Right colon	[redacted]	[redacted]	[redacted]
Unknown vs. Right colon	[redacted]	[redacted]	[redacted]
Number of organs involved (<=2 vs 3+)	[redacted]	[redacted]	[redacted]
Presence of liver metastases (yes vs no)	[redacted]	[redacted]	[redacted]
Number of prior regimens for metastatic disease (1 vs 2+)	[redacted]	[redacted]	[redacted]
Prior use of oxaliplatin (yes vs no)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CRP, C-reactive protein; OS, overall survival; ULN, upper limit of normal.
Source: Table 14.2-2.8.1, CSR efficacy addendum 19th December 2019 (1).

Table 41: Stratified multivariate cox regression model for ORR Enco with cetuximab vs control, FAS (n numbers not available)

	Hazard ratio	***95% CI***	***p-value (2-sided)***
Full cox regression model			
Enco with cetuximab vs. control	[redacted]	[redacted]	[redacted]
Covariates			
Gender (Male vs. Female)	[redacted]	[redacted]	[redacted]
Age (<65 vs. >=65 years)	[redacted]	[redacted]	[redacted]
Removal of primary tumour			
Complete resection vs. Partially resected or not removed	[redacted]	[redacted]	[redacted]

	Hazard ratio	95% CI	p-value (2-sided)
Baseline CRP (<=ULN vs. >ULN)	[redacted]	[redacted]	[redacted]
Side of tumour			[redacted]
Left Colon vs. Right Colon	[redacted]	[redacted]	[redacted]
Left/Right Colon vs. Right Colon	[redacted]	[redacted]	[redacted]
Unknown vs. Right Colon	[redacted]	[redacted]	[redacted]
Number of organs involved (<=2 vs 3+)	[redacted]	[redacted]	[redacted]
Presence of liver metastases (yes vs no)	[redacted]	[redacted]	[redacted]
Prior oxaliplatin vs. No prior oxaliplatin	[redacted]	[redacted]	[redacted]
Number of metastatic sites (1 vs 2+)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CRP, C-reactive protein; ORR, overall response rate; ULN, upper limit of normal.
Source: Table 14.2-1.10.2, CSR efficacy addendum 19th December 2019 (1).

Table 42: Stratified multivariate cox regression model for PFS Enco with cetuximab vs control, FAS (n numbers not available)

	Hazard ratio	95% CI	p-value (2-sided)
Full cox regression model			
Enco with cetuximab vs. control	[redacted]	[redacted]	[redacted]
Covariates			
Gender (male vs. Female)	[redacted]	[redacted]	[redacted]
Age (<65 vs. >=65 years)	[redacted]	[redacted]	[redacted]
Removal of primary tumour (complete resection vs. Partial resection/unresected)	[redacted]	[redacted]	[redacted]
Baseline CRP (<=ULN vs. >ULN)	[redacted]	[redacted]	[redacted]
Side of tumour			[redacted]
Left colon vs. Right colon	[redacted]	[redacted]	[redacted]
Left/right colon vs. Right colon	[redacted]	[redacted]	[redacted]
Unknown vs. Right colon	[redacted]	[redacted]	[redacted]
Number of organs involved (<=2 vs 3+)	[redacted]	[redacted]	[redacted]
Presence of liver metastases (yes vs no)	[redacted]	[redacted]	[redacted]
Number of prior regimens for metastatic disease (1 vs 2+)	[redacted]	[redacted]	[redacted]
Prior use of oxaliplatin (yes vs no)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CRP, C-reactive protein; PFS, progression-free survival; ULN, upper limit of normal.
Source: Table 14.2-3.9.2, CSR efficacy addendum 19th December 2019 (1).

A10. Document B, Section B.2.7.3.1, Figure 4: the figure shows that more events had occurred in the ENCO+CETUX arm than in the Control arm (167 vs 147) despite a hazard ratio of 0.44 in favour of ENCO+CETUX. Please explain this result.

The HR favouring Enco with cetuximab can be explained by the early occurrences of PFS events in the control arm, as shown by the median PFS (4.27 months in the Enco with cetuximab arm vs 1.54 in the control arm) and in Table 43. Moreover, more censoring occurred in the control arm (Source: Table 14.2-3.6.1 (1)). The difference between Enco with cetuximab and control is mainly due to withdrawal of consent ([redacted] patients in the control arm vs [redacted] patients in the Enco with cetuximab arm).

Table 43: PFS for Enco with cetuximab vs control – FAS

	Enco with cetuximab (N=220)	***Control (N=221)***
Patients event-free probability estimates, % (95% CI)		
2 months	[redacted]	[redacted]
4 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
8 months	[redacted]	[redacted]
10 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
14 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval.
Source: Table 14.2-3.1.1, CSR efficacy addendum 19th December 2019 (1).

A11. Please provide the 95% CIs and significance level of the differences between the arms for the patient reported outcomes of CS Document B, Section B.2.7.6.

Hazard ratios and 95% CIs for time to definitive 10% deterioration in EORTC QLQ-C30, FACT-C and EQ-5D domains/scales are provided in Table 44. P-values are not available.

95% CIs and p-values are not available for PGIC data for which proportions of patients achieving "much improved" or "very much improved" at different treatment cycles were provided in the Company Submission.

Table 44: Overall summary of time to definitive 10% deterioration in PRO scales (FAS)

	Enco with cetuximab vs. control
	Hazard ratio (95% CI)
EORTC QLQ-C30	
Global health status	[redacted]
Physical functioning	[redacted]
Emotional functioning	[redacted]
Social functioning	[redacted]
Role functioning	[redacted]
Cognitive functioning	[redacted]
FACT-C	
Functional well-being	[redacted]
Physical well-being	[redacted]
Social/family well-being	[redacted]
Emotional well-being	[redacted]
Colorectal cancer subscale	[redacted]
FACT-C total score	[redacted]
FACT-G total score	[redacted]
Trial outcome index	[redacted]
EQ-5D	
VAS	[redacted]
Utility index	[redacted]

Abbreviations: CI, confidence interval; PFS, progression-free survival.

A12. CS Document B, Section B.2.10.3, Table 12: the sub-column heading for the hazard ratio 2.56 (1.23, 5.26) is shown as 'PFS'. The ERG considers this likely to be a typo and it should read 'OS'. Please confirm.

We can confirm this is a typo and PFS should read OS. See revised table below.

Table 45: Grouped nodes ITC results: Enco with cetuximab vs. FOLFIRI

Intervention	***ITC HR (95% CI)***		***ITC HR (95% CI)***	
	OS	***PFS***	***OS***	***PFS***
Enco with cetuximab	*0.39 (0.19, 0.81)*	*0.30 (0.14, 0.68)*	*comparator*	*comparator*
FOLFIRI	*comparator*	*comparator*	*2.56 (1.23, 5.26)*	*3.33 (1.47, 7.14)*

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; vs., versus.
†Results presented in both directions for ease of interpretation (with FOLFIRI as comparator for comparison with BEACON CRC results, and with Enco with cetuximab as comparator for application in the cost-effectiveness model).

A13. Please present CS Document B, Section 2.11.1.2, Tables 15, 16 and 17, BEACON AEs, with the control arm split into two columns: (1) FOLFIRI+cetuximab patients, and (2) irinotecan+cetuximab patients.

Analyses are provided for the overall summary of AEs (Table 46), individual AEs (Table 47) and individual serious AEs (Table 48) for the overall trial population.

Note that patients are analysed as randomised in the FAS (which is why they are only split into FOLFIRI with cetuximab and irinotecan with cetuximab for FAS analyses), whereas they are analysed as treated in the Safety Set; three patients were treated only with cetuximab based on physician's choice.

Table 46: Overall summary of AEs (Safety set)

		Irinotecan with cetuximab (N=85)	***FOLFIRI with cetuximab (N=105)***	***CETUX (N=3)***
Patients with on treatment death [a]		[redacted]	[redacted]	[redacted]
Patients with AEs leading to death on treatment [b]		[redacted]	[redacted]	[redacted]
AEs	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
AEs, treatment-related (suspected)	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Serious AEs	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Serious AEs, treatment-related (suspected)	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
AEs requiring additional therapy [c]	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
AEs requiring dose interruption of any study drug	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
AEs requiring dose reduction of any study drug	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation of any study drug	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation of all study treatment	*All Grades*	[redacted]	[redacted]	[redacted]

		Irinotecan with cetuximab (N=85)	FOLFIRI with cetuximab (N=105)	CETUX (N=3)
	Grade 3+	[redacted]	[redacted]	[redacted]

Abbreviations: AE; adverse event.
[a] Deaths on-treatment are deaths during treatment or within 30 days of last study treatment.
[b] AEs leading to death on treatment only considers AEs occurring during treatment or within 30 days of the last study medication where outcome is fatal and death occurs within 30 days after last dose of study drug. Patients who had a fatal AE starting on treatment or <30 days of last dose that died >=30 days post last dose are not included in the Death on treatment summary.
[c] Additional therapy includes all non drug therapies and concomitant medications.

Table 47: AEs, regardless of causality, by preferred term – overall (>=10% in any treatment arm) or grade 3+ (>=2% in any treatment arm) (Safety set)

		Irinotecan with cetuximab (N=85)	FOLFIRI with cetuximab (N=105)	CETUX (N=3)
Any AE	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Diarrhoea	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Dermatitis acneiform	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Nausea	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Vomiting	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Decreased appetite	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Abdominal pain	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Fatigue	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Asthenia	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Constipation	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Stomatitis	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Pyrexia	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]

		Irinotecan with cetuximab (N=85)	***FOLFIRI with cetuximab (N=105)***	***CETUX (N=3)***
Rash	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Anaemia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Hypokalaemia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Paronychia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Alopecia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Back pain	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Neutropenia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Dry skin	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Dyspnoea	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Pulmonary embolism	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
White blood cell count decreased	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Hyponatraemia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Ileus	*All Grades*	[redacted]	[redacted]	[redacted]

		Irinotecan with cetuximab (N=85)	***FOLFIRI with cetuximab (N=105)***	***CETUX (N=3)***
	Grade 3+	[redacted]	[redacted]	[redacted]
Febrile neutropenia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Proctalgia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Small intestinal obstruction	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Hypocalcaemia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Intestinal obstruction	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Septic shock	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Subileus	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Acute kidney injury	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Anaphylactic reaction	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Cardio-respiratory arrest	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
General physical health deterioration	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Hypertension	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Malnutrition	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]

Abbreviations: AE; adverse event.
Preferred terms are presented by descending order of frequency in the irinotecan with cetuximab all grades column down to 10% incidence. For all additional AEs, their presentation is determined by AEs (any grade) that occurred in the FOLFIRI with cetuximab >=10% or in the cetuximab only >=10% or any Grade 3+ AE that occurred in either arm at >=2%.

Table 48: Serious AEs, regardless of causality, by preferred term – overall and grades 3+ (>1% in any treatment arm) (Safety set)

		Irinotecan with cetuximab (N=85)	*FOLFIRI with cetuximab (N=105)*	*CETUX (N=3)*
Any SAE	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Diarrhoea	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Pulmonary embolism	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Abdominal pain	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Febrile neutropenia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Vomiting	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Ileus	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Infusion related reaction	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Small intestinal obstruction	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Abdominal infection	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Anal abscess	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Analgesic therapy	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Bacteraemia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Bile duct obstruction	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Bile duct stenosis	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Campylobacter gastroenteritis	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Constipation	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]

		Irinotecan with cetuximab (N=85)	***FOLFIRI with cetuximab (N=105)***	***CETUX (N=3)***
Decreased appetite	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Dyspnoea	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Enterocolitis	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Febrile infection	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Fistula	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Hepatic function abnormal	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Ischaemic stroke	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Jaundice	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Large intestine perforation	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Nausea	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Pain	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Pericarditis	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Peripheral artery stenosis	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Peritonitis	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Pneumocystis jirovecii pneumonia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Prerenal failure	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Proctalgia	*All Grades*	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Rib fracture	*All Grades*	[redacted]	[redacted]	[redacted]

		Irinotecan with cetuximab (N=85)	FOLFIRI with cetuximab (N=105)	CETUX (N=3)
	Grade 3+	[redacted]	[redacted]	[redacted]
Septic shock	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Subileus	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Tumour associated fever	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Tumour pain	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Urinary tract infection	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Acute kidney injury	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Anaphylactic reaction	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Cardio-respiratory arrest	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Drug hypersensitivity	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
General physical health deterioration	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Hypokalaemia	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Intestinal obstruction	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Respiratory failure	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]
Sepsis	All Grades	[redacted]	[redacted]	[redacted]
	Grade 3+	[redacted]	[redacted]	[redacted]

Abbreviations: AE; adverse event.
Preferred terms are presented by descending order of frequency in the irinotecan with cetuximab all grades column, followed by any additional AEs (all grades) that occurred in the FOLFIRI with cetuximab>=1% or in the cetuximab only >=1%.

Information related to study selection in systematic reviews

A14. Please provide a list/table of references for the 52 studies excluded from the clinical evidence RCT review because they reported on first-line therapy (CS Document B Appendices, Appendix D.1.1.3.2).

52 distinct studies (49 reported in 72 full publications and three reported in conference abstracts) reported on first-line treatment and are listed in Table 49.

Table 49: RCT search included studies (first-line studies)

Author	Year	Title	Journal	Volume	Issue	Page
Publications						
1. *Adams RA, Meade AM, Seymour MT, Wilson RH, Madi A, Fisher D, et al*	*2011*	*Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial*	*Lancet Oncol*	*12*	*7*	*642-53*
2. *Aranda, P. Garcia-Alfonso, M. Benavides, A. Sanchez Ruiz, C. Guillen-Ponce, M. J. Safont, J. Alcaide, A. Gomez, R. Lopez, J. L. Manzano, M. Mendez Urena, J. Sastre, F. Rivera, C. Gravalos, T. Garcia, J. I. Martin-Valades, E. Falco, M. Navalon, E. Gonzalez Flores, A. Ma Garcia Tapiador, A. Ma Lopez Munoz, E. Barrajon, M. Reboredo, P. Garcia Teijido, A. Viudez, N. Cardenas, E. Diaz-Rubio and T. Spanish Cooperative Group for the Treatment of Digestive*	*2018*	*First-line mFOLFOX plus cetuximab followed by mFOLFOX plus cetuximab or single-agent cetuximab as maintenance therapy in patients with metastatic colorectal cancer: Phase II randomised MACRO2 TTD study*	*European Journal of Cancer*	*101*		*263-272*
3. *Berlin, J. C. Bendell, L. L. Hart, I. Firdaus, I. Gore, R. C. Hermann, M. F. Mulcahy, M. M. Zalupski, H. M. Mackey, R. L. Yauch, R. A. Graham, G. L. Bray and J. A. Low*	*2013*	*A randomized phase II trial of vismodegib versus placebo with FOLFOX or FOLFIRI and bevacizumab in patients with previously untreated metastatic colorectal cancer*	*Clinical Cancer Research*	*19*	*1*	*258-67*

Author	Year	Title	Journal	Volume	Issue	Page
4. Bokemeyer, C. H. Kohne, F. Ciardiello, H. J. Lenz, V. Heinemann, U. Klinkhardt, F. Beier, K. Duecker, J. H. van Krieken and S. Tejpar	2015	FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer	European Journal of Cancer	51	10	1243-52
5. Bokemeyer, I. Bondarenko, A. Makhson, J. T. Hartmann, J. Aparicio, F. de Braud, S. Donea, H. Ludwig, G. Schuch, C. Stroh, A. H. Loos, A. Zubel and P. Koralewski	2009	Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer	Journal of Clinical Oncology	27	5	663-71
6. Bokemeyer, I. Bondarenko, J. T. Hartmann, F. de Braud, G. Schuch, A. Zubel, I. Celik, M. Schlichting and P. Koralewski	2011	Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study	Annals of Oncology	22	7	1535-46
7. Bokemeyer C, Cutsem EV, Rougier P, Ciardiello F, Heeger S, Schlichting M, et al	2012	Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: Pooled analysis of the CRYSTAL and OPUS randomised clinical trials.	European Journal of Cancer	48	10	1466-75
8. Brodowicz, T. E. Ciuleanu, D. Radosavljevic, E. Shacham-Shmueli, D. Vrbanec, S. Plate, Z. Mrsic-Krmpotic, M. Dank, G. Purkalne, D. Messinger and C. C. Zielinski	2013	FOLFOX4 plus cetuximab administered weekly or every second week in the first-line treatment of patients with KRAS wild-type metastatic colorectal cancer: a randomized phase II CECOG study	Annals of Oncology	24	7	1769-77
9. Carrato, A. Abad, B. Massuti, C. Gravalos, P. Escudero, F. Longo-Munoz, J. L. Manzano, A. Gomez, M. J. Safont, J. Gallego, B. Garcia-Paredes, C. Pericay, R. Duenas, F. Rivera, F. Losa, M. Valladares-Ayerbes, E. Gonzalez and E. Aranda	2017	First-line panitumumab plus FOLFOX4 or FOLFIRI in colorectal cancer with multiple or unresectable liver metastases: A randomised, phase II trial (PLANET-TTD)	European Journal of Cancer	81		191-202
10. Cremolini, C. Antoniotti, S. Lonardi, G. Aprile, F. Bergamo, G. Masi, R. Grande, G. Tonini, C. Mescoli, G. G. Cardellino, L. Coltelli, L. Salvatore, D. C. Corsi, C. Lupi, D. Gemma, M. Ronzoni, E. Dell'Aquila, F. Marmorino, F. Di Fabio, M. L. Mancini, L. Marcucci, G. Fontanini, V. Zagonel, L. Boni and A. Falcone	2018	Activity and Safety of Cetuximab Plus Modified FOLFOXIRI Followed by Maintenance With Cetuximab or Bevacizumab for RAS and BRAF Wild-type Metastatic Colorectal Cancer: A Randomized Phase 2 Clinical Trial	JAMA Oncology	4	4	529-536
11. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al	2015	FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and	Lancet Oncology	16	13	1306-15

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		molecular subgroup analyses of the open-label, phase 3 TRIBE study				
12. De Bruijn MT, Raats DA, Tol J, Hinrichs J, Teerenstra S, Punt CJ, et al	2011	Combined KRAS and TP53 mutation status is not predictive in CAPOX-treated metastatic colorectal cancer.	Anticancer Research	31	4	1379-85
13. Diaz-Rubio E, Gomez-Espana A, Massuti B, Sastre J, Reboredo M, Manzano JL, et al	2012	Role of Kras status in patients with metastatic colorectal cancer receiving first-line chemotherapy plus bevacizumab: a TTD group cooperative study	PLoS ONE	7	10	e47345
14. Douillard, S. Siena, J. Cassidy, J. Tabernero, R. Burkes, M. Barugel, Y. Humblet, G. Bodoky, D. Cunningham, J. Jassem, F. Rivera, I. Kocakova, P. Ruff, M. Blasinska-Morawiec, M. Smakal, J. L. Canon, M. Rother, K. S. Oliner, M. Wolf and J. Gansert	2010	Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study	Journal of Clinical Oncology	28	31	4697-705
15. Douillard, S. Siena, J. Cassidy, J. Tabernero, R. Burkes, M. Barugel, Y. Humblet, G. Bodoky, D. Cunningham, J. Jassem, F. Rivera, I. Kocakova, P. Ruff, M. Blasinska-Morawiec, M. Smakal, J. L. Canon, M. Rother, K. S. Oliner, Y. Tian, F. Xu and R. Sidhu	2014	Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer	Annals of Oncology	25	7	1346-55
16. Douillard, T. Zemelka, G. Fountzilas, C. Barone, M. Schlichting, J. Heighway, S. P. Eggleton and V. Srimuninnimit	2014	FOLFOX4 with cetuximab vs. UFOX with cetuximab as first-line therapy in metastatic colorectal cancer: The randomized phase II FUTURE study	Clinical Colorectal Cancer	13	1	14-26.e1
17. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M	2013	Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer	New England Journal of Medicine	369	11	1023-1034
18. Oki E, Emi Y, Yamanaka T, Uetake H, Muro K, Takahashi T	2019	Randomised phase II trial of mFOLFOX6 plus bevacizumab versus mFOLFOX6 plus cetuximab as first-line treatment for colorectal liver metastasis (ATOM trial)	British Journal of Cancer			
19. Hurwitz HI, Yi J, Ince W, Novotny WF, Rosen O	2009	The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-ras mutation status: analysis of a phase III study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer.	Oncologist	14	1	22-28

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20. Goey, S. G. Elias, H. van Tinteren, M. M. Lacle, S. M. Willems, G. J. A. Offerhaus, W. W. J. de Leng, E. Strengman, A. J. Ten Tije, G. M. Creemers, A. van der Velden, F. E. de Jongh, F. L. G. Erdkamp, B. C. Tanis, C. J. A. Punt and M. Koopman	2017	Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal cancer: updated results and molecular subgroup analyses of the phase 3 CAIRO3 study	Annals of Oncology	28	9	2128-2134
21. Guren, M. Thomsen, E. H. Kure, H. Sorbye, B. Glimelius, P. Pfeiffer, P. Osterlund, F. Sigurdsson, I. M. B. Lothe, A. M. Dalsgaard, E. Skovlund, T. Christoffersen and K. M. Tveit	2017	Cetuximab in treatment of metastatic colorectal cancer: final survival analyses and extended RAS data from the NORDIC-VII study	British Journal of Cancer	116	10	1271-1278
22. Hagman, J. E. Frodin, A. Berglund, J. Sundberg, L. W. Vestermark, M. Albertsson, E. Fernebro and A. Johnsson	2016	A randomized study of KRAS-guided maintenance therapy with bevacizumab, erlotinib or metronomic capecitabine after first-line induction treatment of metastatic colorectal cancer: the Nordic ACT2 trial	Annals of Oncology	27	1	140-7
23. Hecht, E. Mitchell, T. Chidiac, C. Scroggin, C. Hagenstad, D. Spigel, J. Marshall, A. Cohn, D. McCollum, P. Stella, R. Deeter, S. Shahin and R. G. Amado	2009	A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer	Journal of Clinical Oncology	27	5	672-80
24. Heinemann, L. F. von Weikersthal, T. Decker, A. Kiani, U. Vehling-Kaiser, S. E. Al-Batran, T. Heintges, C. Lerchenmuller, C. Kahl, G. Seipelt, F. Kullmann, M. Stauch, W. Scheithauer, J. Hielscher, M. Scholz, S. Muller, H. Link, N. Niederle, A. Rost, H. G. Hoffkes, M. Moehler, R. U. Lindig, D. P. Modest, L. Rossius, T. Kirchner, A. Jung and S. Stintzing	2014	FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial	Lancet Oncology	15	10	1065-75
25. Hurwitz, B. R. Tan, J. A. Reeves, H. Xiong, B. Somer, H. J. Lenz, H. S. Hochster, F. Scappaticci, J. F. Palma, R. Price, J. J. Lee, A. Nicholas, N. Sommer and J. Bendell	2018	Phase II Randomized Trial of Sequential or Concurrent FOLFOXIRI-Bevacizumab Versus FOLFOX-Bevacizumab for Metastatic Colorectal Cancer (STEAM)	Oncologist	14		14
26. Ince, A. M. Jubb, S. N. Holden, E. B. Holmgren, P. Tobin, M. Sridhar, H. I. Hurwitz, F. Kabbinavar, W. F. Novotny, K. J. Hillan and H. Koeppen	2005	Association of k-ras, b-raf, and p53 status with the treatment effect of bevacizumab	Journal of the National Cancer Institute	97	13	981-9

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27. Innocenti F, Ou F-S, Qu X, Zemla TJ, Niedzwiecki D, Tam R,	2019	Mutational Analysis of Patients With Colorectal Cancer in CALGB/SWOG 80405 Identifies New Roles of Microsatellite Instability and Tumor Mutational Burden for Patient Outcome.	J Clin Oncol.	37	14	1227
28. Jonker, P. A. Tang, H. Kennecke, S. A. Welch, M. C. Cripps, T. Asmis, H. Chalchal, A. Tomiak, H. Lim, Y. J. Ko, E. X. Chen, T. Alcindor, J. R. Goffin, G. J. Korpanty, H. Feilotter, M. S. Tsao, A. Theis, D. Tu and L. Seymour	2018	A Randomized Phase II Study of FOLFOX6/Bevacizumab With or Without Pelareorep in Patients With Metastatic Colorectal Cancer: IND.210, a Canadian Cancer Trials Group Trial	Clinical Colorectal Cancer	17	3	231-239.e7
29. Lambrechts, B. Thienpont, V. Thuillier, X. Sagaert, M. Moisse, G. Peuteman, C. Pericay, G. Folprecht, J. Zalcberg, C. Zilocchi, E. Margherini, M. Chiron and E. Van Cutsem	2015	Evaluation of efficacy and safety markers in a phase II study of metastatic colorectal cancer treated with aflibercept in the first-line setting	British Journal of Cancer	113	7	1027-34
30. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al	2014	Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer	N Engl J Med	371	17	1609-18
31. Maughan TS, Meade AM,	2014	A feasibility study testing four hypotheses with phase II outcomes in advanced colorectal cancer (MRC FOCUS3): a model for randomised controlled trials in the era of personalised medicine?	British Journal of Cancer	110	9	2178-86
32. Maughan, R. A. Adams, C. G. Smith, A. M. Meade, M. T. Seymour, R. H. Wilson, S. Idziaszczyk, R. Harris, D. Fisher, S. L. Kenny, E. Kay, J. K. Mitchell, A. Madi, B. Jasani, M. D. James, J. Bridgewater, M. J. Kennedy, B. Claes, D. Lambrechts, R. Kaplan, J. P. Cheadle and M. C. T. Investigators	2011	Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial	Lancet	377	9783	2103-14
33. Modest, A. Jung, N. Moosmann, R. P. Laubender, C. Giessen, C. Schulz, M. Haas, J. Neumann, S. Boeck, T. Kirchner, V. Heinemann and S. Stintzing	2012	The influence of KRAS and BRAF mutations on the efficacy of cetuximab-based first-line therapy of metastatic colorectal cancer: an analysis of the AIO KRK-0104-trial	International Journal of Cancer	131	4	980-6
34. Modest, L. Fischer von Weikersthal, T. Decker, U. Vehling-Kaiser, J. Uhlig, M. Schenk, J. Freiberg-Richter, B. Peuser, C. Denzlinger, C. Peveling Genannt Reddemann, U. Graeven, G. Schuch, I. Schwaner, A. Stahler, A. Jung, T.	2019	Sequential Versus Combination Therapy of Metastatic Colorectal Cancer Using Fluoropyrimidines, Irinotecan, and Bevacizumab: A Randomized, Controlled Study-XELAVIRI (AIO KRK0110)	Journal of Clinical Oncology	37	1	22-32

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36. Nakayama, A. Mitsuma, Y. Sunagawa, K. Ishigure, H. Yokoyama, T. Matsui, H. Nakayama, K. Nakata, A. Ishiyama, T. Asada, S. Umeda, K. Ezaka, N. Hattori, H. Takami, D. Kobayashi, C. Tanaka, M. Kanda, S. Yamada, M. Koike, M. Fujiwara, T. Fujii, K. Murotani, Y. Ando and Y. Kodera	2018	Randomized Phase II Trial of CapOX plus Bevacizumab and CapIRI plus Bevacizumab as First-Line Treatment for Japanese Patients with Metastatic Colorectal Cancer (CCOG-1201 Study)	Oncologist	23	8	919-927
37. Ocvirk, T. Brodowicz, F. Wrba, T. E. Ciuleanu, G. Kurteva, S. Beslija, I. Koza, Z. Papai, D. Messinger, U. Yilmaz, Z. Faluhelyi, S. Yalcin, D. Papamichael, M. Wenczl, Z. Mrsic-Krmpotic, E. Shacham-Shmueli, D. Vrbanec, R. Esser, W. Scheithauer and C. C. Zielinski	2010	Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial	World Journal of Gastroenterology	16	25	3133-43
38. Passardi A, Nanni O, Tassinari D, Turci D, Cavanna L, Fontana A, et a	2015	Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial	Annals of oncology	26		1201
39. Personeni, L. Rimassa, C. Verusio, S. Barni, L. Rubino, S. Bozzarelli, E. Villa, C. Carnaghi, M. C. Tronconi, C. Gerardi, F. Galli, I. Floriani, A. Destro, C. Raschioni, R. Labianca and A. Santoro	2015	FOLFIRI and Cetuximab Every Second Week for First-Line Treatment of KRAS Wild-Type Metastatic Colorectal Cancer According to Phosphatase and Tensin Homolog Expression: A Phase II Study	Clinical Colorectal Cancer	14	3	162-9
40. Price, J. E. Hardingham, C. K. Lee, A. Weickhardt, A. R. Townsend, J. W. Wrin, A. Chua, A. Shivasami, M. M. Cummins, C. Murone and N. C. Tebbutt	2011	Impact of KRAS and BRAF Gene Mutation Status on Outcomes From the Phase III AGITG MAX Trial of Capecitabine Alone or in Combination With Bevacizumab and Mitomycin in Advanced Colorectal Cancer	Journal of Clinical Oncology	29	19	2675-82

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42. Qin, J. Li, L. Wang, J. Xu, Y. Cheng, Y. Bai, W. Li, N. Xu, L. Z. Lin, Q. Wu, Y. Li, J. Yang, H. Pan, X. Ouyang, W. Qiu, K. Wu, J. Xiong, G. Dai, H. Liang, C. Hu, J. Zhang, M. Tao, Q. Yao, J. Wang, J. Chen, S. P. Eggleton and T. Liu	2018	Efficacy and Tolerability of First-Line Cetuximab Plus Leucovorin, Fluorouracil, and Oxaliplatin (FOLFOX-4) Versus FOLFOX-4 in Patients With RAS Wild-Type Metastatic Colorectal Cancer: The Open-Label, Randomized, Phase III TAILOR Trial	Journal of Clinical Oncology			JCO201878318 3
43. Reinacher-Schick A, Schulmann K, Modest DP, Bruns N, Graeven U, Jaworska M,	2012	Effect of KRAS codon13 mutations in patients with advanced colorectal cancer (advanced CRC) under oxaliplatin containing chemotherapy. Results from a translational study of the AIO colorectal study group	BMC Cancer	12		349
44. Richman, M. T. Seymour, P. Chambers, F. Elliott, C. L. Daly, A. M. Meade, G. Taylor, J. H. Barrett and P. Quirke	2009	KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the MRC FOCUS trial	Journal of Clinical Oncology	27	35	5931-7
45. Bennett, Z. Zhao, B. Barber, X. Zhou, M. Peeters, J. Zhang, F. Xu, J. Wiezorek and J. Y. Douillard	2011	Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment	British Journal of Cancer	105	10	1495-502
46. Rivera, M. Karthaus, J. R. Hecht, I. Sevilla, F. Forget, G. Fasola, J. L. Canon, X. Guan, G. Demonty and L. S. Schwartzberg	2017	Final analysis of the randomised PEAK trial: overall survival and tumour responses during first-line treatment with mFOLFOX6 plus either panitumumab or bevacizumab in patients with metastatic colorectal carcinoma	International Journal of Colorectal Disease	32	8	1179-1190
47. Saltz, S. Badarinath, S. Dakhil, B. Bienvenu, W. G. Harker, G. Birchfield, L. K. Tokaz, D. Barrera, P. R. Conkling, M. A. O'Rourke, D. A. Richards, D. Reidy, D. Solit, E. Vakiani, M. Capanu, A. Scales, F. Zhan, K. A. Boehm, L. Asmar and A. Cohn	2012	Phase III trial of cetuximab, bevacizumab, and 5-fluorouracil/leucovorin vs. FOLFOX-bevacizumab in colorectal cancer	Clinical Colorectal Cancer	11	2	101-11
48. Schmiegel, A. Reinacher-Schick, D. Arnold, S. Kubicka, W. Freier, G. Dietrich, M. Geissler, S.	2013	Capecitabine/irinotecan or capecitabine/oxaliplatinin combination with bevacizumab is effective andsafe as first-	Annals of Oncology	24	6	1580-1587

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49. Schwartzberg, F. Rivera, M. Karthaus, G. Fasola, J. L. Canon, J. R. Hecht, H. Yu, K. S. Oliner and W. Y. Go	2014	PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer	Journal of Clinical Oncology	32	21	2240-7
50. Aparicio T, Ghiringhelli F, Boige V, Le Malicot K, Taieb J, Bouche O	2018	Bevacizumab Maintenance Versus No Maintenance During Chemotherapy-Free Intervals in Metastatic Colorectal Cancer: A Randomized Phase III Trial (PRODIGE 9)	Journal of clinical oncology	36	7	674
51. Cardone C, Martinelli E, Troiani T, Sforza V, Avallone A, Nappi A	2019	Exploratory findings from a prematurely closed international, multicentre, academic trial: RAVELLO, a phase III study of regorafenib versus placebo as maintenance therapy after first-line treatment in RAS wild-type metastatic colorectal cancer.	ESMO Open.	4	4	e000519
52. Siena, J. Tabernero, G. Bodoky, D. Cunningham, F. Rivera, P. Ruff, J. L. Canon, R. Koukakis, G. Demonty, G. Hechmati and J. Y. Douillard	2016	Quality of life during first-line FOLFOX4+/-panitumumab in RAS wild-type metastatic colorectal carcinoma: results from a randomised controlled trial	ESMO Open	1	2	e000041
53. Smith, L. Brooks, P. M. Hoff, G. McWalter, S. Dearden, S. R. Morgan, D. Wilson, J. D. Robertson and J. M. Jurgensmeier	2013	KRAS mutations are associated with inferior clinical outcome in patients with metastatic colorectal cancer, but are not predictive for benefit with cediranib	European Journal of Cancer	49	10	2424-32
54. Stintzing, D. P. Modest, L. Rossius, M. M. Lerch, L. F. von Weikersthal, T. Decker, A. Kiani, U. Vehling-Kaiser, S. E. Al-Batran, T. Heintges, C. Lerchenmuller, C. Kahl, G. Seipelt, F. Kullmann, M. Stauch, W. Scheithauer, S. Held, C. Giessen-Jung, M. Moehler, A. Jagenburg, T. Kirchner, A. Jung, V. Heinemann and F.-. investigators	2016	FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial	Lancet Oncology	17	10	1426-1434
55. Stintzing, L. Miller-Phillips, D. P. Modest, L. Fischer von Weikersthal, T. Decker, A. Kiani, U. Vehling-Kaiser, S. E. Al-Batran, T. Heintges, C. Kahl, G. Seipelt, F. Kullmann, M. Stauch, W. Scheithauer, S. Held, M. Moehler, A.	2017	Impact of BRAF and RAS mutations on first-line efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab: analysis of the FIRE-3 (AIO KRK-0306) study	European Journal of Cancer	79		50-60

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57. Tol, M. Koopman, A. Cats, C. J. Rodenburg, G. J. Creemers, J. G. Schrama, F. L. Erdkamp, A. H. Vos, C. J. van Groeningen, H. A. Sinnige, D. J. Richel, E. E. Voest, J. R. Dijkstra, M. E. Vink-Borger, N. F. Antonini, L. Mol, J. H. van Krieken, O. Dalesio and C. J. Punt	2009	Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer	New England Journal of Medicine	360	6	563-72
58. Tol J, Nagtegaal ID, Punt CJ	2009	BRAF mutation in metastatic colorectal cancer	New England Journal of Medicine	361	1	98-9
59. Tol J, Dijkstra JR, Klomp M, Teerenstra S, Dommerholt M, Vink-Borger ME, et al.	2010	Markers for EGFR pathway activation as predictor of outcome in metastatic colorectal cancer patients treated with or without cetuximab	European Journal of Cancer	46	11	1997-2009
60. Tveit, T. Guren, B. Glimelius, P. Pfeiffer, H. Sorbye, S. Pyrhonen, F. Sigurdsson, E. Kure, T. Ikdahl, E. Skovlund, T. Fokstuen, F. Hansen, E. Hofsli, E. Birkemeyer, A. Johnsson, H. Starkhammar, M. K. Yilmaz, N. Keldsen, A. B. Erdal, O. Dajani, O. Dahl and T. Christoffersen	2012	Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study	Journal of Clinical Oncology	30	15	1755-62
61. Ulivi P, Scarpi E, Chiadini E, Marisi G, Valgiusti M, Capelli L, et al	2017	Right- vs. Left-Sided Metastatic Colorectal Cancer: Differences in Tumor Biology and Bevacizumab Efficacy.	International Journal of Molecular Sciences	18	6	9
62. Van Cutsem, C. H. Kohne, E. Hitre, J. Zaluski, C. R. C. Chien, A. Makhson, G. D'Haens, T. Pinter, R. Lim, G. Bodoky, J. K. Roh, G. Folprecht, P. Ruff, C. Stroh, S. Tejpar, M. Schlichting, J. Nippgen and P. Rougier	2009	Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer	New England Journal of Medicine	360	14	1408-1417

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63. Van Cutsem, C. H. Kohne, I. Lang, G. Folprecht, M. P. Nowacki, S. Cascinu, I. Shchepotin, J. Maurel, D. Cunningham, S. Tejpar, M. Schlichting, A. Zubel, I. Celik, P. Rougier and F. Ciardiello	2011	Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status	Journal of Clinical Oncology	29	15	2011-9
64. Van Cutsem, H. J. Lenz, C. H. Kohne, V. Heinemann, S. Tejpar, I. Melezinek, F. Beier, C. Stroh, P. Rougier, J. H. van Krieken and F. Ciardiello	2015	Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer	Journal of Clinical Oncology	33	7	692-700
65. Venook, D. Niedzwiecki, H. J. Lenz, F. Innocenti, B. Fruth, J. A. Meyerhardt, D. Schrag, C. Greene, B. H. O'Neil, J. N. Atkins, S. Berry, B. N. Polite, E. M. O'Reilly, R. M. Goldberg, H. S. Hochster, R. L. Schilsky, M. M. Bertagnolli, A. B. El-Khoueiry, P. Watson, A. B. Benson, 3rd, D. L. Mulkerin, R. J. Mayer and C. Blanke	2017	Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial	JAMA	317	23	2392-2401
66. Vincent, D. Breadner, D. Soulieres, I. G. Kerr, M. Sanatani, W. Kocha, P. Klimo, M. J. MacKenzie, A. O'Connell, F. Whiston, A. S. Malpage, L. Stitt and S. A. Welch	2017	Phase II trial of capecitabine plus erlotinib versus capecitabine alone in patients with advanced colorectal cancer	Future Oncology	13	9	777-786
67. Wasan, A. M. Meade, R. Adams, R. Wilson, C. Pugh, D. Fisher, B. Sydes, A. Madi, B. Sizer, C. Lowdell, G. Middleton, R. Butler, R. Kaplan, T. Maughan and C.-B. investigators	2014	Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial	Lancet Oncology	15	6	631-9
68. Yamada Y, Denda T, Gamoh M, Iwanaga I, Yuki S, Shimodaira H, et al	2018	S-1 and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer (TRICOLORE): a randomized, open-label, phase III, noninferiority trial.	Annals of oncology	29	3	624
69. Pietrantonio F, Morano F, Corallo S, Miceli R, Lonardi S, Raimondi A	2019	Maintenance Therapy With Panitumumab Alone vs Panitumumab Plus Fluorouracil-Leucovorin in Patients With RAS Wild-Type Metastatic Colorectal Cancer: A Phase 2 Randomized Clinical Trial	JAMA Oncol			
70. Yamaguchi, M. Ando, A. Ooki, F. Beier, S. Guenther, P. von Hohnhorst and E. Van Cutsem	2017	Quality of Life Analysis in Patients With RAS Wild-Type Metastatic Colorectal Cancer Treated With First-Line Cetuximab Plus Chemotherapy	Clinical Colorectal Cancer	16	2	e29-e37

Author	Year	Title	Journal	Volume	Issue	Page
71. Yamazaki K, Nagase M, Tamagawa H, Ueda S, Tamura T, Murata K, et al	2016	Randomized phase III study of bevacizumab plus FOLFIRI and bevacizumab plus mFOLFOX6 as first-line treatment for patients with metastatic colorectal cancer (WJOG4407G).	Annals of oncology	27	8	1539-46
72. Ye, T. S. Liu, L. Ren, Y. Wei, D. X. Zhu, S. Y. Zai, Q. H. Ye, Y. Yu, B. Xu, X. Y. Qin and J. Xu	2013	Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases	Journal of Clinical Oncology	31	16	1931-8
Conference abstracts						
1. Aranda, E. García Alfonso, P. Vieitez, J.	2019	Randomized phase II study on the influence of BRAF and PIK3CA mutations on the efficacy of FOLFIRI plus bevacizumab (Bev) or cetuximab (Cet), as first line therapy of patients (pts) with RAS wild-type metastatic colorectal carcinoma (mCRC) and <3 baseline circulating tumor cells (bCTCs).	Journal of Clinical Oncology Conference	37 (Suppl)		Available from: https://meetinglibrary.asco.org/record/171763/abstract
2. Geissler M, Riera Knorrenschild J, Martens UM	2019	Final results and OS of the randomized phase II VOLFI trial (AIO- KRK0109): mFOLFOXIRI + panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild- type metastatic colorectal cancer (mCRC).	Journal of Clinical Oncology Conference	37 (Abstract 3511)		Available from: https://meetinglibrary.asco.org/record/173356/abstract.
3. Pfeiffer P, Bjerregaard JK, Qvortrup C, Sorbye H, Glimelius B, Kersten C	2019	Updated results of NORDIC 8, a randomised trial of cetuximab every 2 weeks with FOLFIRI or cetuximab with alternating FOLFIRI/FOLFOX in patients with RAS and BRAF wild type metastatic colorectal cancer	Annals of Oncology	30 (Suppl 5)		Available from: https://doi.org/10.1093/annonc/mdz246.027

A15. Please provide a list/table of references for the 181 excluded and 56 included but non-UK publications for the cost-effectiveness SLR (Details of the 8 UK studies have already been provided) (CS Document B Appendices, Appendix G.3).

Cost-effectiveness studies identified for the cost-effectiveness search described in CS Document B Appendices, Appendix G.3:

- *56 included non-UK studies (Table 50)*
- *181 excluded studies at full-paper review (Table 51).*

Table 50: Cost-effectiveness studies search included non-UK studies

1. *Chu JNC, J. Ostvar, S. Torchia, J. A. Reynolds, K. L. Tramontano, A. Gainor, J. F. Chung, D. C. Clark, J. W. Hur, C. Cost-effectiveness of immune checkpoint inhibitors for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer. Cancer. 2019:125(2):278-89*
2. *Gourzoulidis GM, N. Petrakis, D. Souglakos, J. Pentheroudakis, G. Kourlaba, G. Economic evaluation of trifluridine and tipiracil hydrochloride in the treatment of metastatic colorectal cancer in Greece. Journal of Comparative Effectiveness Research. 2019:8(3):133-42*
3. *Li Q, Zhang M. Fruquintinib or regorafenib as the third-line treatments for metastatic colorectal cancer based on CONCUR and FRESCO trials: A cost-effectiveness analysis. Journal of Clinical Oncology. 2019:37(15_suppl):e15011-e11*
4. *Mlcoch T, Hrnciarova T, Tuzil J, et al. Propensity Score Weighting Using Overlap Weights: A New Method Applied to Regorafenib Clinical Data and a Cost-Effectiveness Analysis. Value in Health. 2019:22(12):1370-77*
5. *Sherman SKL, J. J. Dahdaleh, F. S. Rajeev, R. Gamblin, T. C. Polite, B. N. Turaga, K. K. Cost-effectiveness of Maintenance Capecitabine and Bevacizumab for Metastatic Colorectal Cancer. JAMA Oncology. 2019:5(2):236-42*
6. *Wong WWL, Zargar M, Berry SR, et al. Cost-effectiveness analysis of selective first-line use of biologics for unresectable RAS wild-type left-sided metastatic colorectal cancer. Curr Oncol. 2019:26(5):e597-e609*
7. *Zhang PF, Wen F, Zhou J, et al. Cost-effectiveness analysis of capecitabine plus bevacizumab versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer from Chinese societal perspective. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2019*
8. *Cho SKH, J. W. Barzi, A. Cost-effectiveness Analysis of Regorafenib and TAS-102 in Refractory Metastatic Colorectal Cancer in the United States. Clinical Colorectal Cancer. 2018:17(4):e751-e61*
9. *Graham CNC, A. Knox, H. N. Sabatelli, L. Hechmati, G. Garawin, T. Strickler, J. H. A within-trial cost-effectiveness analysis of panitumumab compared with bevacizumab in the first-line treatment of patients with wild-type RAS metastatic colorectal cancer in the US. Journal of Medical Economics. 2018:21(11):1075-83*
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11. *Uyl-de Groot CAvR, E. M. Punt, C. J. A. Pescott, C. P. Real-world cost-effectiveness of cetuximab in the third-line treatment of metastatic colorectal cancer based on patient chart review in the Netherlands. Health Economics Review. 2018:8(1):13*

12. Xu YH, J. W. Barzi, A. Impact of drug substitution on cost of care: An example of economic analysis of cetuximab versus panitumumab 14 Economics 1402 Applied Economics. Cost Effectiveness and Resource Allocation. 2018:16(1):30

13. Carvalho ACL, F. Sasse, A. D. Cost-effectiveness of cetuximab and panitumumab for chemotherapy-refractory metastatic colorectal cancer. PLoS ONE. 2017:12(4):e0175409

14. Franken MD, van Rooijen EM, May AM, et al. Cost-effectiveness of capecitabine and bevacizumab maintenance treatment after first-line induction treatment in metastatic colorectal cancer. European journal of cancer (Oxford, England : 1990). 2017:75204-12

15. Goldstein DAC, Q. Ayer, T. Chan, K. K. W. Virik, K. Hammerman, A. Brenner, B. Flowers, C. R. Hall, P. S. Bevacizumab for metastatic colorectal cancer: A global cost-effectiveness analysis. Oncologist. 2017:22(6):694-99

16. Parikh RCD, X. L. Robert, M. O. Lairson, D. R. Cost-effectiveness of treatment sequences of chemotherapies and targeted biologics for elderly metastatic colorectal cancer patients. Journal of Managed Care and Specialty Pharmacy. 2017:23(1):64-73

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Table 51: Cost-effectiveness studies search excluded studies

1. J. R. Sabater, L. Batteson, R. McCarthy, G. Wex, J. Vera, S. R. M. Becquart, M. Mounedji, N. Taieb, J. Peeters, M. Falcone, A. Validation of cost-effectiveness of trifluridine/tipiracil versus best supportive care and regorafenib for previously treated metastatic colorectal cancer in the UK using phase IIIb PRECONNECT early access clinical trial data in the real world setting. (2019) Journal of Clinical Oncology 37; Supplement 4
2. Z. J. C. Lee, S. L. Tan, G. Soo, K. C. Teo, C. C. M. Cost Effectiveness of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Management of Colorectal Peritoneal Carcinomatosis. (2018) Annals of Surgical Oncology 25; 8; 2340-2346
3. T. D. M. Hamilton, A. J. Lim, H. Hunink, M. G. M. Cost-Effectiveness Analysis of Cytoreductive Surgery and HIPEC Compared With Systemic Chemotherapy in Isolated Peritoneal Carcinomatosis From Metastatic Colorectal Cancer. (2019) Annals of Surgical Oncology 26; 4; 1110-1117
4. M. K. C. Seo, J. Do cancer biomarkers make targeted therapies cost-effective? A systematic review in metastatic colorectal cancer. (2018) PLoS ONE 13; 9; e0204496
5. J. N. C. Chu, J. G. Ostvar, S. Torchia, J. A. Reynolds, K. L. Gainor, J. F. Chung, D. C. Clark, J. W. Hur, C. Cost-effectiveness of nivolumab vs. ipilimumab/nivolumab vs. trifluridine/tipiracil or mFOLFOX6/cetuximab for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer. (2018) Journal of Clinical Oncology 36; 15 Supplement 1;
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10. J. N. C. Chu, J. G. Ostvar, S. Torchia, J. A. Reynolds, K. L. Gainor, J. F. Chung, D. C. Clark, J. W. Hur, C. Nivolumab versus nivolumab with ipilimumab versus trifluridine/tipiracil for metastatic microsatellite instability-high colorectal cancer: A modeling decision analysis. (2018) Journal of Clinical Oncology 36; 4 Supplement 1;
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12. S. L. Zhu, J. Sun, W. Xuan, J. Budget Impact Analysis of Regorafenib in the Third-Line Treatment of Patients with Metastatic Colorectal Cancer. (2018) Value in Health 21; Supplement 2; S12
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181. Stereotactic Body Radiotherapy for Oligometastatic Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness. (2019)

A16. Please provide a list/table of references for the 204 studies excluded at full text screening stage of the health-related quality of life SLR (CS Document B Appendices, Appendix H3).

Health-related quality of life studies identified and excluded (N=204) at full screening are provided in Table 52.

Table 52: Health-related quality of life studies identified and excluded (N=204)

Author	Title	Journal	Year	Citation
1. Allaix, M. E.	Long-term functional results and quality of life after transanal endoscopic microsurgery	Colorectal Disease	2011	6):20.
2. Ameri, H.	Mapping EORTC-QLQ-C30 and QLQ-CR29 onto EQ-5D-5L in Colorectal Cancer Patients	Journal Of Gastrointestinal Cancer.	2019	
3. Ameri, H.	Mapping the cancer-specific QLQ-C30 onto the generic EQ-5D-5L and SF-6D in colorectal cancer patients	Expert Review Of Pharmacoeconomics And Outcomes Research	2019	19(1):89-96.
4. Andersson, J.	Health-related quality of life after laparoscopic and open surgery for rectal cancer in a randomized trial	The British Journal Of Surgery	2013	100(7):941-949.
5. Anota, A.	Erlotinib added to bevacizumab as maintenance therapy and health-related quality of life in patients with metastatic colorectal cancer: Results of the GERCOR DREAM phase III trial	Quality Of Life Research	2016	25 (1 Supplement 1):112.
6. Antonuzzo, L.	Bevacizumab plus XELOX as first-line treatment of metastatic colorectal cancer: The OBELIX study	World Journal Of Gastroenterology	2015	21(23):7281-7288.
7. Asplund, D.	Persistent perineal morbidity is common following abdominoperineal excision for rectal cancer	International Journal Of Colorectal Disease	2015	30(11):1563-1570.
8. Augestad, K. M.	Cost-effectiveness and quality of life in surgeon versus general practitioner-organised colon cancer surveillance: A randomised controlled trial	BMJ Open	2013	3 (4) (no pagination)(e002391).
9. Augestad, K. M.	Should the surgeon or the general practitioner (GP) follow up patients after surgery for colon cancer? A randomized controlled trial protocol focusing on quality of life, cost-effectiveness and serious clinical events	BMC Health Services Research	2008	8 (no pagination)(137).
10. Bednarski, B. K.	Randomized clinical trial of accelerated enhanced recovery after minimally invasive colorectal cancer surgery (RecoverMI trial)	British Journal Of Surgery	2019	106(10):1311-1318.

11. Benedict, A.	Quality of Life of Patients Living with Metastatic Colorectal Cancer (Mcrc): European Organization for Research and Treatment of Cancer (Eortc) Questionnaire Results from a Real World European Survey	Value In Health	2018	21 (Supplement 3):S80.
12. Best, J. H.	Preference values associated with stage III colon cancer and adjuvant chemotherapy	Quality Of Life Research	2010	1-10.
13. Bossema, E. R.	Evaluation of the treatment tradeoff method in rectal cancer patients: is surgery preference related to outcome utilities?	Medical Decision Making	2008	28(6):888-98.
14. Bouvier, A. M.	Adjuvant treatments do not alter the quality of life in elderly patients with colorectal cancer: a population-based study	Cancer	2008	113(4):879-86.
15. Boyd, K. A.	Analysis of adverse events and quality of life data for an economic evaluation of adjuvant chemotherapy in colorectal cancer: When can we stop collecting?	Trials. Conference: Clinical Trials Methodology Conference	2011	12(SUPPL. 1).
16. Boyd, N. F.	Whose utilities for decision analysis?	Medical Decision Making	1990	10(1):58-67.
17. Brigic, A.	Functional outcomes and related quality of life following colonic resection for neoplasia: A case-controlled study	Colorectal Disease	2013	1):32.
18. Brigic, A.	A prospective case control study of functional outcomes and related quality of life after colectomy for neoplasia	International Journal Of Colorectal Disease	2017	32(6):777-787.
19. Brookes, M. J.	The use of pre-operative intravenous iron improves post-operative patient reported quality of life in anaemic colorectal cancer patients: Results from a multicentre randomised controlled trial	Gut	2017	66 (Supplement 2):A105-A106.
20. Brown, S. R.	The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery	Annals Of Surgery	2014	259(5):916-923.
21. Carter HE, Z. D., John Simes R, Schofield DJ, Howard K, Zalcberg JR, Price TJ, Tebbutt NC	The cost effectiveness of bevacizumab when added to capecitabine, with or without mitomycin-C, in first line treatment of metastatic colorectal cancer: results from the Australasian phase III MAX study	European Journal Of Cancer (Oxford, England :	2014	1990) 50(3):535-543.
22. Chang, J.	Effects of regorafenib (REG) therapy on health-related quality of life (HRQoL) in patients with metastatic colorectal cancer (mCRC) in the phase III CONCUR trial	Journal Of Clinical Oncology. Conference	2015	33(15 SUPPL. 1).
23. Charlton, M. E.	Long-term quality of life (QoL) for stage II/III rectal cancer survivors in the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)	Journal Of Clinical Oncology. Conference	2014	32(3 SUPPL. 1).

24. Charlton, M. E.	Predictors of long-term quality of life for survivors of stage II/III rectal cancer in the cancer care outcomes research and surveillance consortium	Journal Of Oncology Practice	2015	11(4):e476-e486.
25. Colwell HH, M. S., Turner MP, Lu J, Wright N, Peeters M, Cella D, Devercelli G	Psychometric evaluation of the FACT Colorectal Cancer Symptom Index (FCSI-9): reliability, validity, responsiveness, and clinical meaningfulness	Oncologist	2010	15(3):308-316.
26. Couwenberg, A. M.	Utility scores and preferences for surgical and organ-sparing approaches for treatment of intermediate and high-risk rectal cancer	Diseases Of The Colon And Rectum	2018	61(8):911-919.
27. Dang, H.	Quality of life and fear of cancer recurrence in T1 colorectal cancer patients treated with endoscopic or surgical tumor resection	Gastrointestinal Endoscopy	2019	89(3):533-544.
28. Diouf, M.	Could baseline health-related quality of life (QoL) improve prognostication of overall survival in metastatic colorectal cancer? Results from GERCOR OPTIMOX 1 study	Journal Of Clinical Oncology. Conference: ASCO Annual Meeting	2011	29(15 SUPPL. 1).
29. Diouf M, C. B., Filleron T, Tournigand C, Hug de Larauze M, Garcia-Larnicol ML, Dumont S, Louvet C, Perez-Staub N, Hadengue A, de Gramont A, Bonnetain F	Could baseline health-related quality of life (QoL) predict overall survival in metastatic colorectal cancer? The results of the GERCOR OPTIMOX 1 study	Health And Quality Of Life Outcomes	2014	12(69).
30. Dominitz, J. A.	Patient preferences and quality of life associated with colorectal cancer screening	American Journal Of Gastroenterology	1997	92(12):2171-2178.
31. Doornebosch, P. G.	Impact of transanal endoscopic microsurgery on functional outcome and quality of life	International Journal Of Colorectal Disease	2008	23(7):709-13.
32. Doornebosch, P. G.	Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer	Colorectal Disease	2007	9(6):553-8.
33. Douillard, J. Y.	Final skin toxicity (ST) and patient-reported outcomes (PRO) results from PRIME: A randomized phase III study of panitumumab (pmab) plus FOLFOX4 (CT) for first-line metastatic colorectal cancer (mCRC)	Journal Of Clinical Oncology. Conference	2012	30(4 SUPPL. 1).
34. Downing, A.	Functional Outcomes and Health-Related Quality of Life After Curative Treatment for Rectal Cancer: A Population-Level Study in England	International Journal Of Radiation Oncology Biology Physics	2019	103(5):1132-1142.

35. Downing, A.	Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis	Journal Of Clinical Oncology	2015	33(6):616-24.
36. Dranitsaris, G.	A pharmacoeconomic modeling approach to estimate a value-based price for new oncology drugs in Europe	Journal Of Oncology Pharmacy Practice	2012	18(1):57-67.
37. Dranitsaris, G.	The application of pharmacoeconomic modelling to estimate a value-based price for new cancer drugs	Journal Of Evaluation In Clinical Practice	2012	18(2):343-51.
38. Dranitsaris, G.	Using pharmacoeconomic modelling to determine value-based pricing for new pharmaceuticals in malaysia	Malaysian Journal Of Medical Sciences	2011	18(4):31-42.
39. Dranitsaris, G.	Improving patient access to cancer drugs in India: Using economic modeling to estimate a more affordable drug cost based on measures of societal value	International Journal Of Technology Assessment In Health Care	2011	27(1):23-30.
40. Drury, A.	The cost of survival: an exploration of colorectal cancer survivors' experiences of pain	Acta Oncologica	2017	56(2):205-211.
41. Drury, A.	The cost of survival: A mixed-method exploration of healthcarerelated factors predicting colorectal cancer survivors' quality of life	Annals Of Oncology	2018	29 (Supplement 8):viii689.
42. Ducreux, M.	A prospective, observational trial to assess the safety and efficacy of regorafenib in patients with metastatic colorectal cancer (mCRC) in routine clinical practice (CORRELATE)	Annals Of Oncology	2015	4):iv91-iv92.
43. Escobar, A.	Influence of anxiety and depression on 1-year health related quality of life in colorectal cancer patients	Value In Health	2013	16 (7):A421-A422.
44. Farkkil a, N.	HRQoL in different health states of colorectal cancer	European Journal Of Cancer	2011	1):S263.
45. Farkkila, N.	Health-related quality of life in colorectal cancer	Colorectal Disease	2013	15(5):e215-e222.
46. Farkkila, N.	Health-related quality of life among breast, prostate, and colorectal cancer patients with end-stage disease	Quality Of Life Research : An International Journal Of Quality Of Life Aspects Of Treatment, Care And Rehabilitation	2014	23(4):1387-1394.
47. Foster, C.	Quality of life, health and personal wellbeing up to two years following curative intent colorectal cancer surgery: Results from the UK colorectal wellbeing (CREW) study	Supportive Care In Cancer	2015	1):S316.

48. Fusco F, W. J., Gray A, Chau I, Dunham L, Love S, Roberts A, Moschandreas J, Virdee P, Lewington V, Wilson G, Khan N, Francis A, Wasan H, Sharma R	Selective internal radiotherapy (SIRT) in metastatic colorectal cancer patients with liver metastases: preliminary primary care resource use and utility results from the foxfire randomised controlled trial	Value In Health	2017	20(9):A445-A446.
49. Gadan, S.	Does a Defunctioning Stoma Impair Anorectal Function after Low Anterior Resection of the Rectum for Cancer? A 12-Year Follow-up of a Randomized Multicenter Trial	Diseases Of The Colon And Rectum	2017	60(8):800-806.
50. Glaser, A. W.	Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: A cross-sectional survey	BMJ Open	2013	3 (4) (no pagination)(e002317).
51. Gonzalez, E.	Health related quality of life and physical function after abdominoperineal resection for rectal cancer	Colorectal Disease	2011	6):35.
52. Gonzalez-Barba, F.	Relation of QLQ-C30 and QLQ-CR29 health related quality of life scales and biochemical indicators of nutritional status	Value In Health	2017	20 (9):A455-A456.
53. Gordon LG, P. T., Kularatna S, Hawkes AL	A telephone-delivered multiple health behaviour change intervention for colorectal cancer survivors: making the case for cost-effective healthcare	European Journal Of Cancer Care	2015	24(6):854-861.
54. Gosselink, M. P.	Quality of life after total mesorectal excision for rectal cancer	Colorectal Disease	2006	8(1):15-22.
55. Graham, C. N.	A within-trial cost-effectiveness analysis of panitumumab compared with bevacizumab in the first-line treatment of patients with wild-type RAS metastatic colorectal cancer in the US	Journal Of Medical Economics	2018	21(11):1075-1083.
56. Graham, J.	A pilot study of subjective well-being in colorectal cancer patients and their caregivers	Patient Related Outcome Measures	2017	8:111-119.
57. Gray, A. M.	Quality of life in patients with liver metastases from colorectal cancer treated with first-line selective internal radiotherapy (SIRT): Results from the FOXFIRE prospective randomized studies	Annals Of Oncology	2017	28 (Supplement 5):v201.
58. Gurland, B.	Using technology to facilitate data capture and integration of Patient Reported Outcomes (PRO) into colorectal surgical practice	Diseases Of The Colon And Rectum	2010	53 (4):691.
59. H, A.	Quality of life advantages demonstrated for patients receiving Tomudex compared with those receiving 5-fluorouracil plus leucovorin (5 FU+LV) in the treatment of advanced colorectal cancer (ACC)	Proc Eur Cancer Conf	1099	

60. Haapamaki, M. M.	Physical performance and quality of life after extended abdominoperineal excision of rectum and reconstruction of the pelvic floor with gluteus maximus flap	Diseases Of The Colon And Rectum	2011	54(1):101-106.
61. Hall, P. S.	Costs of cancer care for use in economic evaluation: A UK analysis of patient-level routine health system data	British Journal Of Cancer	2015	112(5):948-956.
62. Hamashima, C.	Long-term quality of life of postoperative rectal cancer patients	Journal Of Gastroenterology And Hepatology (Australia)	2002	17(5):571-576.
63. Harpreet, W.	Overall survival analysis of the FOXFIRE-SIRFLOX-FOXFIRE global prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer	Annals Of Oncology	2017	28 (Supplement 3):iii148.
64. Haviland, J.	Trajectories of quality of life, health and personal well-being in the first 2 years following curative intent colorectal cancer: Results from the UK colorectal wellbeing (CREW) Study	Psycho-Oncology	2015	2):91-92.
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Missing materials in the Reference Pack

A17. Please provide full text of the following 2 references, missing from the Reference Pack:

1. *Pierre Fabre. Data-On-File_4.0 NCRA_SACTregimenanalysis_130220*

41. *Pierre Fabre. Data-On-File_3.0 IPSOS Healthcare Physician Survey_online_Oct 2019.*

References have been provided as separate documents, as requested.

Section B: Clarification on cost-effectiveness data

Data related to economic model

B1. Priority question: Please present the reconstructed OS IPD that underlies the estimates of CS Document B, Section B.3.3.1.4.2, Table 34.

The reconstructed OS IPD for the trifluridine-tipiracil raw OS curve is presented below in Table 53. Please note that there will be some discrepancies between the estimated IPD presented below and the true IPD from the trial; this is because the number of patients at risk was only known at specific time points as presented in Figure 1 in the trial publication (Mayer 2015 (2)).

Table 53: Reconstructed OS IPD for trifluridine-tipiracil (from Mayer 2015)

Timepoint (months)	*N at risk*	*Events*	
		Censored	*Death*
0	*534*	*0*	*0*
0.2691	*530*	*0*	*4*
0.4326	*528*	*0*	*2*
0.6001	*527*	*0*	*1*
0.9843	*520*	*0*	*7*
1.1029	*518*	*0*	*2*
1.2499	*517*	*0*	*1*
1.3358	*516*	*0*	*1*
1.393	*514*	*0*	*2*
1.4298	*513*	*0*	*1*
1.4748	*512*	*0*	*1*
1.5442	*511*	*0*	*1*
1.57285	*510*	*1*	*0*
1.6015	*507*	*0*	*3*
1.6383	*505*	*0*	*2*
1.9244	*499*	*0*	*6*
2.0307	*497*	*0*	*2*
2.092	*495*	*0*	*2*
2.137	*493*	*0*	*2*
2.1861	*490*	*0*	*3*
2.2229	*488*	*0*	*2*
2.272	*485*	*0*	*3*
2.3211	*483*	*0*	*2*
2.3865	*481*	*0*	*2*

Timepoint (months)	N at risk	Events	
		Censored	Death
2.4642	478	0	3
2.5419	475	0	3
2.5951	472	0	3
2.7177	470	0	2
2.779	467	0	3
2.8608	465	0	2
2.8977	460	0	5
2.9794	459	0	1
3.098	454	0	5
3.2084	451	0	3
3.23095	450	1	0
3.2535	446	0	4
3.3026	440	0	6
3.3721	438	0	2
3.42525	437	1	0
3.4784	435	0	2
3.51935	434	1	0
3.5603	427	0	7
3.6155	426	1	0
3.6707	420	0	6
3.7648	415	0	5
3.81185	414	1	0
3.8589	410	0	4
3.8998	409	1	0
3.9407	405	0	4
4.0389	399	0	6
4.0818	398	1	0
4.1247	394	0	4
4.1861	390	0	4
4.22905	389	1	0
4.272	385	0	4
4.3517	384	1	0
4.4314	381	0	3
4.48455	380	1	0
4.5377	377	0	3
4.5807	376	1	0
4.6237	370	0	6
4.7137	365	0	5
4.7383	364	1	0

Timepoint (months)	N at risk	Events	
		Censored	Death
4.7629	357	0	7
4.8284	352	0	5
4.88155	351	1	0
4.9347	346	0	5
4.9879	345	1	0
5.0411	340	0	5
5.1433	337	0	3
5.19845	336	1	0
5.2536	334	0	2
5.3068	333	1	0
5.36	327	0	6
5.4337	322	0	5
5.4542	321	1	0
5.4747	314	0	7
5.5319	313	1	0
5.5891	312	0	1
5.6628	304	0	8
5.76905	302	2	0
5.8753	299	0	3
5.93665	298	1	0
5.998	294	0	4
6.133	289	0	5
6.1882	287	2	0
6.2434	281	0	6
6.28635	278	3	0
6.3293	274	0	4
6.3947	271	3	0
6.4601	268	0	3
6.5112	265	3	0
6.5623	262	0	3
6.61755	260	2	0
6.6728	256	0	4
6.728	253	3	0
6.7832	247	0	6
6.818	245	2	0
6.8528	240	0	5
6.86515	239	1	0
6.8775	234	0	5
6.97145	230	4	0

Timepoint (months)	N at risk	Events	
		Censored	Death
7.1267	226	4	0
7.188	224	0	2
7.2207	223	1	0
7.2534	221	0	2
7.2841	219	2	0
7.3148	215	0	4
7.3761	212	3	0
7.4374	210	0	2
7.50485	207	3	0
7.5723	204	0	3
7.6275	201	3	0
7.6827	199	0	2
7.7338	196	3	0
7.7849	193	0	3
7.80335	192	1	0
7.8218	188	0	4
7.877	185	3	0
7.9322	183	0	2
7.9833	181	2	0
8.0344	178	0	3
8.09575	174	4	0
8.1571	171	0	3
8.2756	165	6	0
8.3941	164	0	1
8.4554	161	3	0
8.5167	159	0	2
8.5923	155	4	0
8.6679	153	0	2
8.74555	149	4	0
8.8232	147	0	2
8.88865	144	3	0
8.9541	141	0	3
9.04195	137	4	0
9.1298	136	0	1
9.2076	132	0	4
9.2526	131	1	0
9.2976	126	0	5
9.38345	124	2	0
9.4693	123	0	1

Timepoint (months)	N at risk	Events	
		Censored	Death
9.5633	120	3	0
9.6573	118	0	2
9.7472	116	2	0
9.8371	115	0	1
9.88415	114	1	0
9.9312	110	0	4
10.00275	108	2	0
10.0743	105	0	3
10.13355	104	1	0
10.1928	103	0	1
10.25005	102	1	0
10.3073	100	0	2
10.35635	99	1	0
10.4054	98	0	1
10.4688	96	2	0
10.5322	92	0	4
10.59555	91	1	0
10.6589	90	0	1
10.69975	89	1	0
10.7406	88	0	1
10.88975	84	4	0
11.0676	83	1	0
11.0963	79	0	4
11.1576	78	1	0
11.2189	77	0	1
11.2863	75	2	0
11.3537	74	0	1
11.413	73	1	0
11.4723	72	0	1
11.52745	71	1	0
11.5826	70	0	1
11.7481	66	4	0
11.9136	65	0	1
11.96875	64	1	0
12.0239	63	0	1
12.13015	62	1	0
12.2938	58	0	4
12.3837	57	1	0
12.4736	56	0	1

Timepoint (months)	N at risk	Events	
		Censored	Death
12.5595	55	0	1
12.61465	54	1	0
12.6698	53	0	1
12.7475	51	0	2
12.84965	50	1	0
13.0785	48	2	0
13.2052	47	0	1
13.34205	46	1	0
13.4789	45	0	1
13.55455	44	1	0
13.6302	43	0	1
13.716	42	1	0
13.8018	41	0	1
13.857	40	1	0
13.9122	38	0	2
14.0104	37	0	1
14.07785	36	1	0
14.1453	34	0	2
14.2271	33	0	1
14.5131	30	3	0
14.7991	29	0	1
15.37925	23	6	0
16.16375	22	1	0
16.3681	20	0	2
16.62755	18	2	0
17.12	16	2	0
17.353	13	0	3
18.9545	0	13	0

B2. Priority question: Please present the reconstructed PFS IPD that underlies the estimates of CS Document B, Section B.3.3.1.4.2, Table 35.

The reconstructed OS IPD for the trifluridine-tipiracil raw PFS curve is presented below in Table 54. As for the reconstructed OS curves, please note that there will be some discrepancies between the estimated IPD presented below and the true IPD from the trial publication (Mayer 2015 (2)).

Table 54: Reconstructed PFS IPD for trifluridine-tipiracil (from Mayer 2015)

Timepoint (months)	N at risk	Events	
		Censored	Progression
0	534	0	0
0.3069	530	0	4
0.4532	528	0	2
0.5274	524	0	4
0.6016	519	0	5
0.6943	517	0	2
0.8035	511	0	6
0.9066	505	0	6
1.0138	499	0	6
1.0797	494	0	5
1.121	489	0	5
1.1766	485	0	4
1.2405	480	0	5
1.3209	477	0	3
1.3457	467	0	10
1.3891	460	0	7
1.4447	456	0	4
1.4715	452	0	4
1.5398	426	0	26
1.575	413	0	13
1.6122	404	0	9
1.6432	389	0	15
1.6661	370	0	19
1.693	359	0	11
1.7221	336	0	23
1.7493	299	0	37
1.7907	281	0	18
1.8238	270	0	11
1.8569	257	0	13
1.8734	252	0	5

Timepoint (months)	N at risk	Events	
		Censored	Progression
1.9415	245	0	7
1.9828	238	0	7
2.0652	233	0	5
2.21455	232	1	0
2.2424	229	0	3
2.3186	226	0	3
2.3825	224	0	2
2.42885	223	1	0
2.4752	221	0	2
2.5432	220	0	1
2.60395	219	1	0
2.6647	217	0	2
2.74505	216	1	0
2.8697	215	1	0
2.914	211	0	4
3.0026	210	0	1
3.0541	209	1	0
3.1056	207	0	2
3.1653	204	0	3
3.2096	203	1	0
3.2539	201	0	2
3.2808	195	0	6
3.3014	189	0	6
3.3427	186	0	3
3.36845	185	1	0
3.3942	181	0	4
3.4705	173	0	8
3.4912	164	0	9
3.5201	158	0	6
3.549	154	0	4
3.5717	153	1	0
3.5944	149	0	4
3.615	143	0	6
3.7036	139	0	4
3.71605	138	1	0
3.7285	127	0	11
3.80575	126	1	0
3.883	125	0	1
3.9634	121	0	4

Timepoint (months)	N at risk	Events	
		Censored	Progression
4.0458	117	0	4
4.2682	116	0	1
4.29605	115	1	0
4.3239	114	0	1
4.5927	113	1	0
4.6823	112	0	1
4.83365	110	2	0
4.985	109	0	1
5.0098	103	0	6
5.0675	101	0	2
5.1191	97	0	4
5.1912	91	0	6
5.2139	90	1	0
5.2366	85	0	5
5.2861	82	0	3
5.4179	80	0	2
5.44985	79	1	0
5.4818	75	0	4
5.5313	72	0	3
5.6168	71	1	0
5.7023	70	0	1
5.7641	68	0	2
5.8939	67	0	1
6.01435	66	1	0
6.1348	65	0	1
6.1781	62	0	3
6.347	61	1	0
6.5159	60	0	1
6.6241	59	1	0
6.7323	54	0	5
6.7591	50	0	4
6.8559	49	1	0
6.9527	46	0	3
7.0022	43	0	3
7.0846	42	1	0
7.167	41	0	1
7.2371	35	0	6
7.84575	30	5	0
8.4544	29	0	1

Timepoint (months)	N at risk	Events	
		Censored	Progression
8.4915	28	0	1
8.6789	27	0	1
8.9055	26	0	1
9.14855	25	1	0
9.3916	24	0	1
9.4143	22	0	2
9.59555	21	1	0
9.9437	18	0	3
10.2156	17	0	1
10.4319	16	0	1
10.4752	15	1	0
10.5185	10	0	5
11.3259	5	5	0
12.1333	4	0	1
14.125	3	0	1
16.7068	0	3	0

B3. Priority question: Please provide the BEACON EQ-5D-5L crosswalked to EQ-5D-3L values split by arm, with the control arm split into two columns: (1) FOLFIRI+cetuximab baseline patients, and (2) irinotecan+cetuximab baseline patients, for the following analyses:

- **All EQ-5D values, treating trial baseline as Day=0 (4 tables)**
- **PFS EQ-5D values, treating trial baseline as Day=0 (4 tables)**
- **Post-progression EQ-5D values, treating the 1st EQ-5D 30 day follow-up concurrent to or subsequent to the date of progression as Day=0 (4 tables)**

The additional utility analyses stratified by post-progression timepoint (end of treatment and 30-day follow-up) and number of previous lines of therapy are presented below in Table 55, Table 56, Table 57 and Table 58. Unscheduled visits make it challenging to present utility data in a meaningful way in the format requested (baseline, day 30, day 60 etc); hence the data is presented in a simplified way split by pre-progression, post-progression (all), post-progression (30-day follow-up), post-progression (end of treatment), and all values.

Table 55: Utility values for the BEACON CRC Enco with cetuximab arm

	Enco with cetuximab				
	Pre-progression	***Post-progression: all***	***Post-progression: 30-day follow-up***	***Post-progression: end of treatment***	***All values***
1 or ≥2 prior treatments					
Mean	*0.744*	*0.622*	*0.658*	*0.611*	*0.732*
SD	*0.194*	*0.252*	*0.211*	*0.263*	*0.204*
Min	*-0.429*	*-0.200*	*0.119*	*-0.200*	*-0.429*
Max	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*
95% CI	*0.010*	*0.041*	*0.069*	*0.049*	*0.010*
95% LCI	*0.754*	*0.663*	*0.727*	*0.660*	*0.742*
95% UCI	*0.733*	*0.582*	*0.589*	*0.562*	*0.721*
Records	*1,328*	*147*	*36*	*111*	*1,475*
1 prior treatment					
Mean	*0.740*	*0.622*	*0.630*	*0.619*	*0.729*
SD	*0.198*	*0.248*	*0.247*	*0.251*	*0.206*
Min	*-0.429*	*-0.122*	*0.119*	*-0.122*	*-0.429*
Max	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*
95% CI	*0.013*	*0.048*	*0.097*	*0.056*	*0.013*
95% LCI	*0.753*	*0.670*	*0.727*	*0.675*	*0.741*
95% UCI	*0.728*	*0.573*	*0.533*	*0.562*	*0.716*

	Enco with cetuximab				
	Pre-progression	Post-progression: all	Post-progression: 30-day follow-up	Post-progression: end of treatment	All values
Records	940	101	25	76	1,041
≥2 prior treatments					
Mean	0.752	0.624	0.720	0.593	0.738
SD	0.187	0.261	0.060	0.292	0.200
Min	-0.160	-0.200	0.641	-0.200	-0.200
Max	1.000	1.000	0.836	1.000	1.000
95% CI	0.018	0.075	0.036	0.097	0.019
95% LCI	0.770	0.699	0.756	0.690	0.757
95% UCI	0.733	0.548	0.685	0.497	0.720
Records	395	46	11	35	441

Abbreviations: CI, confidence interval; LCI, lower confidence interval; SD, standard deviation, UCI, upper confidence interval.

Table 56: Utility values for the BEACON CRC control arm

	Control, pooled				
	Pre-progression	Post-progression: all	Post-progression: 30-day follow-up	Post-progression: end of treatment	All values
1 or ≥2 prior treatments					
Mean	0.741	0.631	0.663	0.618	0.717
SD	0.193	0.279	0.275	0.281	0.219
Min	-0.009	-0.352	-0.138	-0.352	-0.352
Max	1.000	1.000	1.000	1.000	1.000
95% CI	0.016	0.043	0.080	0.051	0.016
95% LCI	0.756	0.674	0.742	0.669	0.733
95% UCI	0.725	0.588	0.583	0.567	0.702
Records	591	161	46	115	752
1 prior treatment					
Mean	0.744	0.665	0.739	0.638	0.727
SD	0.195	0.251	0.167	0.270	0.210
Min	-0.009	-0.352	0.338	-0.352	-0.352
Max	1.000	1.000	1.000	1.000	1.000
95% CI	0.019	0.047	0.061	0.059	0.018
95% LCI	0.762	0.712	0.799	0.697	0.745
95% UCI	0.725	0.618	0.678	0.579	0.709
Records	415	110	29	81	525
≥2 prior treatments					
Mean	0.734	0.558	0.533	0.570	0.694

	Control, pooled				
	Pre-progression	Post-progression: all	Post-progression: 30-day follow-up	Post-progression: end of treatment	All values
SD	0.189	0.324	0.369	0.304	0.237
Min	0.003	-0.173	-0.138	-0.173	-0.173
Max	1.000	1.000	1.000	1.000	1.000
95% CI	0.028	0.089	0.176	0.102	0.031
95% LCI	0.762	0.646	0.709	0.672	0.725
95% UCI	0.706	0.469	0.358	0.468	0.663
Records	176	51	17	34	227

Abbreviations: CI, confidence interval; LCI, lower confidence interval; SD, standard deviation, UCI, upper confidence interval.

Table 57: Utility values for the BEACON CRC control arm, FOLFIRI with cetuximab subgroup

	Control, FOLFIRI subgroup				
	Pre-progression	Post-progression: all	Post-progression: 30-day follow-up	Post-progression: end of treatment	All values
1 or ≥2 prior treatments					
Mean	0.741	0.692	0.770	0.663	0.732
SD	0.204	0.246	0.174	0.263	0.214
Min	-0.009	-0.352	0.338	-0.352	-0.352
Max	1.000	1.000	1.000	1.000	1.000
95% CI	0.021	0.052	0.069	0.065	0.020
95% LCI	0.763	0.744	0.839	0.728	0.752
95% UCI	0.720	0.641	0.700	0.598	0.712
Records	350	87	24	63	437
1 prior treatment					
Mean	0.737	0.681	0.752	0.655	0.726
SD	0.201	0.251	0.170	0.271	0.213
Min	-0.009	-0.352	0.338	-0.352	-0.352
Max	1.000	1.000	1.000	1.000	1.000
95% CI	0.023	0.058	0.076	0.074	0.022
95% LCI	0.761	0.739	0.828	0.729	0.748
95% UCI	0.714	0.623	0.676	0.581	0.704
Records	283	71	19	52	354
≥2 prior treatments					
Mean	0.759	0.742	0.835	0.700	0.756
SD	0.219	0.222	0.193	0.229	0.218
Min	0.003	0.155	0.531	0.155	0.003

	Control, FOLFIRI subgroup				
	Pre-progression	Post-progression: all	Post-progression: 30-day follow-up	Post-progression: end of treatment	All values
Max	1.000	1.000	1.000	1.000	1.000
95% CI	0.052	0.109	0.169	0.136	0.047
95% LCI	0.811	0.851	1.004	0.835	0.803
95% UCI	0.707	0.634	0.666	0.564	0.709
Records	67	16	5	11	83

Abbreviations: CI, confidence interval; LCI, lower confidence interval; SD, standard deviation, UCI, upper confidence interval.

Table 58: Utility values for the BEACON CRC control arm, irinotecan with cetuximab subgroup

	Control, irinotecan subgroup				
	Pre-progression	Post-progression: all	Post-progression: 30-day follow-up	Post-progression: end of treatment	All values
1 or ≥2 prior treatments					
Mean	0.740	0.559	0.546	0.564	0.697
SD	0.175	0.300	0.320	0.295	0.224
Min	0.066	-0.173	-0.138	-0.173	-0.173
Max	1.000	1.000	1.000	1.000	1.000
95% CI	0.022	0.068	0.134	0.080	0.025
95% LCI	0.762	0.627	0.680	0.644	0.722
95% UCI	0.718	0.490	0.413	0.484	0.672
Records	241	74	22	52	315
1 prior treatment					
Mean	0.757	0.635	0.713	0.608	0.729
SD	0.181	0.251	0.167	0.271	0.204
Min	0.109	0.054	0.484	0.054	0.054
Max	1.000	1.000	1.000	1.000	1.000
95% CI	0.031	0.079	0.103	0.099	0.031
95% LCI	0.788	0.714	0.817	0.707	0.760
95% UCI	0.726	0.557	0.610	0.510	0.699
Records	132	39	10	29	171
≥2 prior treatments					
Mean	0.719	0.473	0.407	0.507	0.659
SD	0.167	0.330	0.355	0.319	0.241
Min	0.066	-0.173	-0.138	-0.173	-0.173
Max	1.000	1.000	0.906	1.000	1.000
95% CI	0.031	0.109	0.201	0.130	0.039

	Control, irinotecan subgroup				
	Pre-progression	**Post-progression: all**	**Post-progression: 30-day follow-up**	**Post-progression: end of treatment**	**All values**
95% LCI	*0.750*	*0.582*	*0.608*	*0.638*	*0.698*
95% UCI	*0.687*	*0.364*	*0.206*	*0.377*	*0.620*
Records	*109*	*35*	*12*	*23*	*144*

Abbreviations: CI, confidence interval; LCI, lower confidence interval; SD, standard deviation, UCI, upper confidence interval.

B4. Please provide the R code used to generate the results of CS Document B, Section B.3.3.1. For the hazard ratios of B.3.3.1 please present the associated data inputs with full referencing to the original studies, coupled with the necessary arithmetic if this is not within the R code.

An example of the R code used to generate survival curves from the IPD in the submission is presented below. The following packages were used:

- *Flexsurv*
- *Survminer*

Parametric models were fit to the IPD using the following syntax:

EC_OS_llogis_model <- Flexsurvreg(Surv(futime, fustat)~1, data = EC_OS, dist="llogis")

Where "EC_OS_llogis_model" is the object that the parametric model is assigned to, "futime" is the timepoint, "fustat" is the censoring value, EC_OS is the IPD file for Enco with cetuximab OS, and "llogis" indicates that a loglogistic distribution is to be used.

Parameters were extracted from these models using the following methods shown in Table 59.

Table 59: Example R code to generate parametric model parameters used in the economic model

Model outputs	***R code***
Model coefficients	*coef(EC_OS_llogis_model)*
Cholesky decomposition parameters	*chol(vcov(EC_OS_llogis_model))*
Akaike information criterion (AIC)	*AIC(EC_OS_llogis_model)*
Bayesian information criterion (BIC)	*BIC(EC_OS_llogis_model)*

Hazard ratios are applied in the model for two purposes:

- *1. In base-case analyses to generate comparator survival curves for FOLFIRI using survival curves for enco with cetuximab to which hazard ratios of relative effectiveness from the ITC were applied; and*
- *2. In base case/scenario analyses to generate adjusted survival curves for trifluridine-tipiracil, using published survival curves to which hazard ratios for*

the relative impact of the BRAF-mutation (versus non-BRAF-mutation) on OS and PFS were applied.

Data inputs and sources for all hazard ratios applied in the model are provided below, consistent with information already provided in the Company Submission.

1. ITC inputs (Enco with cetuximab vs FOLFIRI: economic base-case analyses)

Table 60: Summary of the trials used to conduct the grouped nodes ITC

Study	Treatment arm	Sample size	Population	Trial reported HR (95% CI)	
				OS	PFS
BEACON CRC (1) Total trial population BRAF-mutant	Enco with cetuximab	220	BRAF-mut	0.61 (0.48, 0.77)	0.44 (0.35, 0.55)
	FOLFIRI with cetuximab or irinotecan with cetuximab	221		comparator	comparator
20050181/ NCT0039183 (3) Trial BRAF-mutant subgroup	FOLFIRI with panitumumab	45 (total across both arms)	BRAF-mut	0.64 (0.32, 1.28)	0.69 (0.32, 1.49)
	FOLFIRI			comparator	comparator

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; CI, confidence interval; Enco, encorafenib; FOLFIRI, folinic acid/fluorouracil/irinotecan; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table 61: Grouped nodes ITC results: Enco with cetuximab vs. FOLFIRI

Intervention	ITC HR (95% CI)		ITC HR (95% CI)	
	OS	PFS	PFS	PFS
Enco with cetuximab	0.39 (0.19, 0.81)	0.30 (0.14, 0.68)	comparator	comparator
FOLFIRI	comparator	comparator	2.56 (1.23, 5.26)	3.33 (1.47, 7.14)

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; vs., versus.
†Results presented in both directions for ease of interpretation (with FOLFIRI as comparator for comparison with BEACON CRC results, and with Enco with cetuximab as comparator for application in the cost-effectiveness model).

2. BRAF-mutant adjustment HRs (Enco with cetuximab vs trifluridine-tipiracil base-case and scenario analysis)

Table 62: BRAF V600E adjustment HRs (Peeters 2015; base-case)

Outcome	HR (95% CI), BRAF wild-type versus BRAF V600E	HR (95% CI), BRAF V600E versus BRAF wild-type (used in model)	Source
OS	0.25 (0.18, 0.36)	4.00 (2.78, 5.56)	Peeters 2015 (3)
PFS	0.28 (0.20, 0.40)	3.57 (2.50, 5.00)	

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table 63: Alternative log HR for OS in BRAF V600E patients versus BRAF wild-type patients (Safaee Ardekani 2012; scenario analysis)

Log HR for OS	HR conversion (used in model)	Source
0.81	2.24	Safaee Ardekani 2012 (4)

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; HR, hazard ratio; OS, overall survival.

B5. The scope specifies that the cost of testing for BRAF V600 mutation should be included. It is not clear from the company submission what the company estimate of this cost is. Please provide the company estimate.

The cost of testing for the BRAF V600E mutation has not been included within the economic analysis. It was not deemed necessary given the cost would apply to both treatment and comparator arms, and as such would be cost neutral in this sense. Pierre Fabre understands that this test is already happening in the majority of treatment centres in the UK (5), and it should be noted that BRAF mutation testing is currently commissioned as part of a "multi-target NGS panel - small variant (KRAS, NRAS, BRAF)", in patients with CRC who may be eligible for anti-EGFR therapy and/or in whom BRAF status is required as per the NICE diagnostic guidance for molecular testing for Lynch syndrome (6).

The 2020/21 National Tariff Payment System – a consultation notice (7), highlights that previously a number of cancer molecular diagnostic tests including the BRAF test were reimbursed outside of national tariff prices, but from 2020-2021 these tests will be reimbursed centrally. We understand that the costs of these tests start from around £85.

B6. Please provide the arithmetic rationale of the cycles' general population survival estimates in worksheet LifeTables cells Y6:Y789, together with an account of the 0% general population survival estimates for those aged 88.4 years and above. If there is an error in the calculations and this has little effect upon results, please only provide the corrected base case estimates.

The model engines should use cells X6:X789 on the LifeTables sheet as transition probabilities for general population mortality directly. However, when this change is made, the results are not impacted. This is because at no point over the time horizon of the model does the general population mortality exceed that of the selected OS curves. The limited time horizon of the model means that no patients reach the age of 88.4 in any scenario.

B7. It would be appreciated if a copy of the survivalCurves worksheet cells B64:G82 could be supplied, with the cells that contain control variables that affect the model output highlighted.

The only cells which affect the model outputs are listed below (please note that the cell references shown refer to the survivalCurves worksheet of the submitted model and not to the embedded colour-coded Excel file):

- *Hazard ratios (cells E70, E75, G70, G75)*
- *Distribution selections (cells B4, C4, E4, B9, C9, E9)*
- *Whether the hazard ratios shown are being used or not (cells D5, D10)*

A highlighted example of the range in question (B64:G82) is included below. The cells which are used in the model are highlighted in green; cells which have no impact are not highlighted.

Table 64: Range B64:G82 from the "survivalCurves" worksheet of the economic model

	E+C	FOLFIRI		Lonsurf	
Overall survival (OS)					
Distribution	*Loglogistic*	*Loglogistic*	*Apply HR instead?*	*Loglogistic*	*Apply HR instead?*
Piecewise?	*No*	*No*	*Yes*	*No*	*No*
Cut-off	*End of K-M*	*End of K-M*	*HR*	*End of K-M*	*HR*
Custom cut-off (weeks)			*2.5641*		*4.0000*
Progression-free survival (PFS)					
Distribution	*Loglogistic*	*Loglogistic*	*Apply HR instead?*	*Loglogistic*	*Apply HR instead?*
Piecewise	*No*	*No*	*Yes*	*No*	*No*
Cut-off	*End of K-M*	*End of K-M*	*HR*	*End of K-M*	*HR*
Custom cut-off (weeks)			*3.3333*		*3.5714*
Time on treatment (ToT)					
Distribution	*Equal to PFS*	*Equal to PFS*	*Apply HR instead?*	*Equal to PFS*	*Apply HR instead?*
Piecewise	*No*	*No*	*Yes*	*No*	*No*
Cut-off	*End of K-M*	*End of K-M*	*HR*	*End of K-M*	*HR*
Custom cut-off (weeks)			*3.3333*		
Stopping rule	*No*	*No*		*No*	
Cut-off (weeks)					

Section C: Textual clarification and additional points

Other clarifications

C1. Please provide a reference for NHS England commissioning 7 laboratories to test all mCRC patients for BRAF V600 mutation from 2021FY.

Pierre Fabre were provided with this insight during an Office for Market Access meeting with NICE and NHS England in 2019, however the national tariff payment consultation system suggests this will be earlier from 2020-21 (7). As described for question B.5, Pierre Fabre understands that this test is already happening in the majority of treatment centres in the UK (5), and it should be noted that BRAF mutation testing is currently commissioned as part of a "multi-target NGS panel - small variant (KRAS, NRAS, BRAF)", in patients with CRC who may be eligible for anti-EGFR therapy and/or in whom BRAF status is required as per the NICE diagnostic guidance for molecular testing for Lynch syndrome (6).

C2. Please provide a table summarising all changes (including which document, page number, location of text) in CIC marking between the documents initially submitted (dated 17 February 2020) and the documents submitted subsequently (dated 25 February 2020 and labelled with 'erratum' in the file names).

Table 65: Summary of changes to AIC/CIC mark-up

Page*	***Nature of confidential information***	***Rationale for confidential status***	***Timeframe of confidentiality restriction‡***
Form A			
Page 28, Table 7, base case result in key scenario analyses table	☒ *Commercial in confidence* ☐ *Academic in confidence* ☐ *Depersonalised data*	*PAS prices not in public domain.*	*Indefinite*
Form B appendices			
Page 150, Figure 8, Health state occupancy providing OS/PFS data	☐ *Commercial in confidence* ☒ *Academic in confidence* ☐ *Depersonalised data*	*BEACON data subject to potential publication.*	*Q4 2020*
Page 152, Table 20, costs by health state, % absolute increment column added in full	☒ *Commercial in confidence* ☐ *Academic in confidence* ☐ *Depersonalised data*	*PAS prices not in public domain.*	*Indefinite*
Page 153, Table 21, resource use by category of cost, % absolute increment column added in full	☒ *Commercial in confidence* ☐ *Academic in confidence* ☐ *Depersonalised data*	*PAS prices not in public domain.*	*Indefinite*
Page 153, Table 23, costs by health state, % absolute increment column added in full	☒ *Commercial in confidence* ☐ *Academic in confidence* ☐ *Depersonalised data*	*PAS prices not in public domain.*	*Indefinite*
Page 154, Table 24, resource use by category of cost, % absolute increment column added in full	☒ *Commercial in confidence* ☐ *Academic in confidence* ☐ *Depersonalised data*	*PAS prices not in public domain.*	*Indefinite*

References

1. Array BioPharma Inc. Clinical study report addendum: A Multicenter, Randomized, Open-label, 3-Arm Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5 Fluorouracil (5-FU)/Folinic Acid (FA)/Irinotecan (FOLFIRI)/Cetuximab with a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients with BRAF V600E mutant Metastatic Colorectal Cancer. Clinical Study ARRAY-818-302. Date of data cut off 15 August 2019. Date of report 19 December 2019.
2. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-19.
3. Peeters M, Oliner KS, Price TJ, Cervantes A, Sobrero AF, Ducreux M, et al. Analysis of KRAS/NRAS Mutations in a Phase III Study of Panitumumab with FOLFIRI Compared with FOLFIRI Alone as Second-line Treatment for Metastatic Colorectal Cancer. Clin Cancer Res. 2015;21(24):5469-79.
4. Safaee Ardekani G, Jafarnejad SM, Tan L, Saeedi A, Li G. The prognostic value of BRAF mutation in colorectal cancer and melanoma: a systematic review and meta-analysis. PLoS One. 2012;7(10):e47054.
5. Pierre Fabre. Data-On-File_1.0 BRAF TESTING 29_01_2020.
6. NHS England. National Genomic Test Directory for rare and inherited disease, March 2019. Available from: https://www.england.nhs.uk/publication/national-genomic-test-directories/. Accessed on: 24 January 2020
7. NHS England and NHS Improvement. 2020/21 National Tariff Payment System – a consultation notice. 2019. Available from: https://improvement.nhs.uk/documents/6257/2021_NTPS_statutory_consultation_notice.pdf. Accessed on: 20 March 2020

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Encorafenib in dual therapy with cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Further clarification questions

Pierre Fabre responses

April 2020

File name	*Version*	*Contains confidential information*	*Date*
ID1598 encorafenib ERG further clarification questions v2.0.docx	*2*	*Yes*	*3 April 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.

Issue 1: The ERG thanks the company for supplying all the requested KM data within the clarification response deadline. The definition of some events is not clear to the ERG, and these definitions may differ between OS, PFS, PPS and TTD. The ERG would be grateful if the following terms could be more clearly defined, with a view to data definitions being applied consistently across the OS, PFS, PPS and TTD KM data. Note that the ERG may have wrongly inferred equivalence between some terms between tables 4, 12, 20 and 28, and would be grateful for any further clarification on the data definitions.

Table 4: OS	Table 12: PFS	Table 20: PPS	Table 28: TTD	ERG interpretation
Ongoing without event	n.a. due to all patients progressing or censored prior to EoS/data cutoff date	Ongoing without event	Cutoff	End of study/censored due to data cut-off date.
Lost to follow-up	Last adequate assessment	Lost to follow-up	Last contact	Lost to follow-up

Reasons for censoring of different events across OS, PFS and PPS are provided in Table 1. Reasons for censoring that are highlighted in teal, although planned, were not observed.

Table 1: Reasons for censoring OS, PFS, PPS

Event	*Reason for censoring*
OS and PPS	*Ongoing without event* *Withdrawal of consent* *Lost to follow-up* *Study termination by sponsor* *Other*
PFS	*No baseline assessment* *No adequate post-baseline assessment* *Subsequent therapy given* *Progression after 2 or more missed assessments* *Death after 2 or more missed assessments* *Last adequate assessment* *Withdrawal of consent* *Ongoing tumour assessments*

As denoted by green text in Table 2 "Ongoing without event" in the OS and PPS tables are equivalent to "Ongoing tumour assessments" in the PFS table

As denoted by red text in Table 2 "Lost to follow-up" in the OS and PPS tables is not equivalent to "Last adequate assessment" in the PFS table. A patient "Lost to follow-up" was always censored at the "Last adequate assessment", however patients who were censored as "Last adequate assessment" (3 patients across Enco with cetuximab and control arms) were not necessarily "Lost to follow-up".

Table 2: Equivalence between reasons for censoring

Table 4: OS	Table 12: PFS	Table 20: PPS	ERG interpretation
Ongoing without event	***Ongoing tumour assessments***	*Ongoing without event*	*End of study/censored due to data cut-off date.*
Lost to follow-up	***Last adequate assessment***	*Lost to follow-up*	*Lost to follow-up*

As described below for Issue 4, the TTD data provided in response to clarification question A.5 (Table 28 to Table 35) was based on the event "discontinuation due to AE" in error, instead of "discontinuation due to any cause". Revised Kaplan-Meier data tables have been provided under Issue 4 (Table 8 to Table 15).

Issue 2: The ERG is grateful for the additional data supplied in the company response to B3. But the ERG asks that the company supplies the EQ-5D data in the format requested. Given the concerns around interim visits, please attribute interim visits to their closest 30 day timepoint.

The EQ-5D records for each time point are reported in Table 3 and are stratified by treatment arm and number of prior treatments. When a utility value was recorded at an unscheduled timepoint (i.e. on day 22 of a treatment cycle instead of day 1), the record was pooled with the nearest scheduled timepoint, e.g. "Cycle 1 day 22" would be treated as a record for "Cycle 2 day 1". The unscheduled visits were mapped against their corresponding closest visit as per the table below.

Table 3: Mapping of unscheduled timepoints to nearest scheduled timepoint

Unscheduled timepoint	*Closest scheduled timepoint*	*Number of unscheduled timepoints*
CYCLE 1 DAY 22 UNSCHEDULED 02	*CYCLE 2 DAY 1*	*1*
CYCLE 2 DAY 8 UNSCHEDULED 01	*CYCLE 2 DAY 1*	*2*
CYCLE 2 DAY 22 UNSCHEDULED 01	*CYCLE 3 DAY 1*	*1*
CYCLE 5 DAY 22 UNSCHEDULED 01	*CYCLE 6 DAY 1*	*1*
CYCLE 5 DAY 22 UNSCHEDULED 02	*CYCLE 6 DAY 1*	*2*
CYCLE 6 DAY 22 UNSCHEDULED 01	*CYCLE 7 DAY 1*	*2*
CYCLE 7 DAY 22 UNSCHEDULED 01	*CYCLE 8 DAY 1*	*1*
CYCLE 12 DAY 22 UNSCHEDULED 01	*CYCLE 13 DAY 1*	*1*
CYCLE 14 DAY 8 UNSCHEDULED 01	*CYCLE 14 DAY 1*	*1*

Summary tables for each treatment cycle are presented below in Table 4, Table 5, Table 6 and Table 7. As previously described, numbered treatment cycle timepoints (I.e. cycles 1 to 25) were pooled to determine PFS utility, and the "End of treatment" and "30 day follow up" timepoints were pooled to determine PPS utility. The analysis was performed on complete cases only.

Table 4: EQ-5D values for the Enco with cetuximab arm of BEACON, 1 or ≥2 prior treatments

Cycle number	*1 or ≥2 prior treatment regimens*			*1 prior treatment regimen*			*≥2 prior treatment regimens*		
	Mean	*SD*	*N*	*Mean*	*SD*	*N*	*Mean*	*SD*	*N*
SCREENING	[redacted]								
1	[redacted]								
2	[redacted]								
3	[redacted]								
4	[redacted]								
5	[redacted]								
6	[redacted]								
7	[redacted]								
8	[redacted]								
9	[redacted]								
10	[redacted]								
11	[redacted]								
12	[redacted]								
13	[redacted]								
14	[redacted]								
15	[redacted]								
16	[redacted]								
17	[redacted]								
18	[redacted]								
19	[redacted]								
20	[redacted]								
21	[redacted]								
22	[redacted]								
23	[redacted]								
24	[redacted]								
25	[redacted]								
END OF TREATMENT	[redacted]								
30 DAY FOLLOW UP	[redacted]								

Table 5: EQ-5D values for the control arm (FOLFIRI and irinotecan patients) of BEACON, 1 or ≥2 prior treatments

Cycle number	1 or ≥2 prior treatment regimens			1 prior treatment regimen			≥2 prior treatment regimens		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
SCREENING	[redacted]								
1	[redacted]								
2	[redacted]								
3	[redacted]								
4	[redacted]								
5	[redacted]								
6	[redacted]								
7	[redacted]								
8	[redacted]								
9	[redacted]								
10	[redacted]								
11	[redacted]								
12	[redacted]								
13	[redacted]								
14	[redacted]								
15	[redacted]								
16	[redacted]								
17	[redacted]								
18	[redacted]								
END OF TREATMENT	[redacted]								
30 DAY FOLLOW UP	[redacted]								

Table 6: EQ-5D values for the control arm (FOLFIRI with cetuximab subgroup) of BEACON, 1 or ≥2 prior treatments

Cycle number	1 or ≥2 prior treatment regimens			1 prior treatment regimen			≥2 prior treatment regimens		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
SCREENING	[redacted]								
1	[redacted]								
2	[redacted]								
3	[redacted]								
4	[redacted]								
5	[redacted]								

Cycle number	1 or ≥2 prior treatment regimens			1 prior treatment regimen			≥2 prior treatment regimens		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
END OF TREATMENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 DAY FOLLOW UP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: EQ-5D values for the control arm (irinotecan with cetuximab subgroup) of BEACON, 1 or ≥2 prior treatments

Cycle number	1 or ≥2 prior treatment regimens			1 prior treatment regimen			≥2 prior treatment regimens		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
SCREENING	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]

Cycle number	1 or ≥2 prior treatment regimens			1 prior treatment regimen			≥2 prior treatment regimens		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
13	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
END OF TREATMENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 DAY FOLLOW UP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Issue 3: During the clarification teleconference with the company, it was highlighted that the R code would need to be provided in sufficient detail, to be able to verify that the functional forms applied in the company Excel model are consistent with the parameters estimated using the R code. The answer to B4 does not provide sufficient detail for this to be done. Please provide the relevant R code to enable this cross check to be performed.

The R code used to specify the parametric curves used is listed below. The code is commented to describe the purpose of each section of code; comments are indicated with hash signs. Lines of code highlighted in teal must be changed to your local directory.

```
#Load libraries and clear variables
rm(list=ls())
library(flexsurv)
library(ggplot2)
library(readxl)
library(xlsx)
library(survminer)
#CHANGE THE FILE PATHS BELOW TO AMEND YOUR DATA
#DATA MUST CONTAIN A TIME VARIABLE AND CENSORING VARIABLE NAMED LIKE SO: "futime", "fustat"
#THE INPUT FILES MUST CONTAIN IPD WITH AT LEAST THE FOLLOWING THREE COLUMNS: PATIENT ID, FOLLOW UP TIME [FUTIME], AND FOLLOW UP STATISTIC [FUSTAT]. THIS EXAMPLE FITS MODELS TO THE PFS CURVES OF THE POOLED BEACON CONTROL ARM AND ENCO WITH CETUXIMAB ARM.
setwd ("C:/Users/Mtech/ID1598//Survival data")
file_path <- "C:/Users/Mtech/ID1598//Survival data"
input_file_list <- c("Control_PFS.xlsx", " Enco_cetux_PFS.xlsx",)
output_file_list <- c("Control_PFS_Output.xlsx", "Enco_cetux_PFS_Output.xlsx")

#Initialise counters
#Model counter
i = 1
#Spacing counter
```

```
j = 1
#Data counter
k = 1
#Filename counter
l = 1
''
#Import datasets

for (l in 1:3) {

        #Create workbook with two main summary sheets for export to Excel
        wb <- createWorkbook()
        sheet1 <- createSheet(wb, sheetName = "Parameter outputs")
        sheet2 <- createSheet(wb, sheetName = "Cholesky outputs")
        sheet3 <- createSheet(wb, sheetName = "Assessment of fit")

        dataset <- read_excel(paste(file_path,input_file_list[l], sep ="/"))

        model_list <- c("gengamma", "weibull", "exp", "llogis", "lnorm", "gompertz")
        worksheet_headings <- c("gengamma", " ", " ", " "," ", " ","weibull", " ", " ", " "," ", " ", "exp", " "," "," "," "," ","llogis", " ", " ", " "," "," ","lnorm", " ", " ", " ", " "," ","gompertz")

        #Loop through each model type, pull out parameters, Cholesky decompositions, assessment of fit, print to summary Excel worksheet, add all other survival data to new sheets

        for (i in 1:6) {

                if (i == 1){

                        fs <- flexsurvreg(Surv(futime, fustat)~1, data = dataset, dist = "gengamma", method = "CG")
```

```
        } else {

                fs <- flexsurvreg(Surv(futime, fustat)~1, data = dataset, dist =
model_list[i])

        }

        parameters <- as.data.frame(coef(fs))
        addDataFrame(parameters, sheet1, startRow = j, startColumn = 2)

        cholesky <- as.data.frame(chol(vcov(fs)))
        addDataFrame(cholesky, sheet2, startRow = j, startColumn = 2)

        aic <- AIC(fs)
        bic <- BIC(fs)

        aicbic <- matrix(c(aic,bic),ncol=2)
        rownames(aicbic)<-c("Values")
        colnames(aicbic)<-c("AIC","BIC")
        addDataFrame(aicbic, sheet3, startRow = j, startColumn = 2)

        j = j + 6

}

#Counter reset for debug purposes

j = 1

i = 1

#Print headings to Excel file and save
```

```
        addDataFrame(worksheet_headings, sheet1, col.names=FALSE,
row.names=FALSE, startRow = 1, startColumn = 1)
        addDataFrame(worksheet_headings, sheet2, col.names=FALSE,
row.names=FALSE, startRow = 1, startColumn = 1)
        addDataFrame(worksheet_headings, sheet3, col.names=FALSE,
row.names=FALSE, startRow = 1, startColumn = 1)

        saveWorkbook(wb, file = output_file_list[l])

        rm(wb, sheet1, sheet2, sheet3)

        l = l + 1

}
```

Issue 4: Initial ERG work suggests that the "*Reason for censoring" within the company clarification response may be incorrect, with particular reference to the TTD KM data. The ERG would be grateful if the company could confirm its labelling of (1) events and (2) * Reason for censoring, for OS, PFS, PPS and TTD in its responses to A2, A3, A4 and A5. If possible, the ERG would also be grateful for the TTD data definitions of "Last contact" and "Treatment End + 30", and of "Subsequent therapy" and how this differs from "Discontinuation".

Labelling for OS, PFS and PPS are correct.

Regarding TTD specifically, the TTD data provided in response to clarification question A.5 (Table 28 to Table 35) were based on the event "discontinuation due to AE" in error, instead of "discontinuation due to any cause". This is why "End of treatment +30" was listed as a reason for censoring and not an event.

A new set of tables for TTD capturing "discontinuation due to any cause" are provided in Table 8 to Table 15. For these data, the only reason for censoring available in the dataset is "Treatment ongoing". All reasons for end of treatment events have also been included.

Table 8: TTD - Events and subjects censored by timepoint - (Safety set – Enco with cetuximab)

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** Reason for censoring.*

[a] Dose interruption = dose interruption of >28 consecutive days (encorafenib or binimetinib) or 2 missed consecutive irinotecan, fluorouracil, or folinic acid or >4 missed consecutive cetuximab doses.

Table 9: TTD - Events and subjects censored by timepoint - (Safety set – Control)

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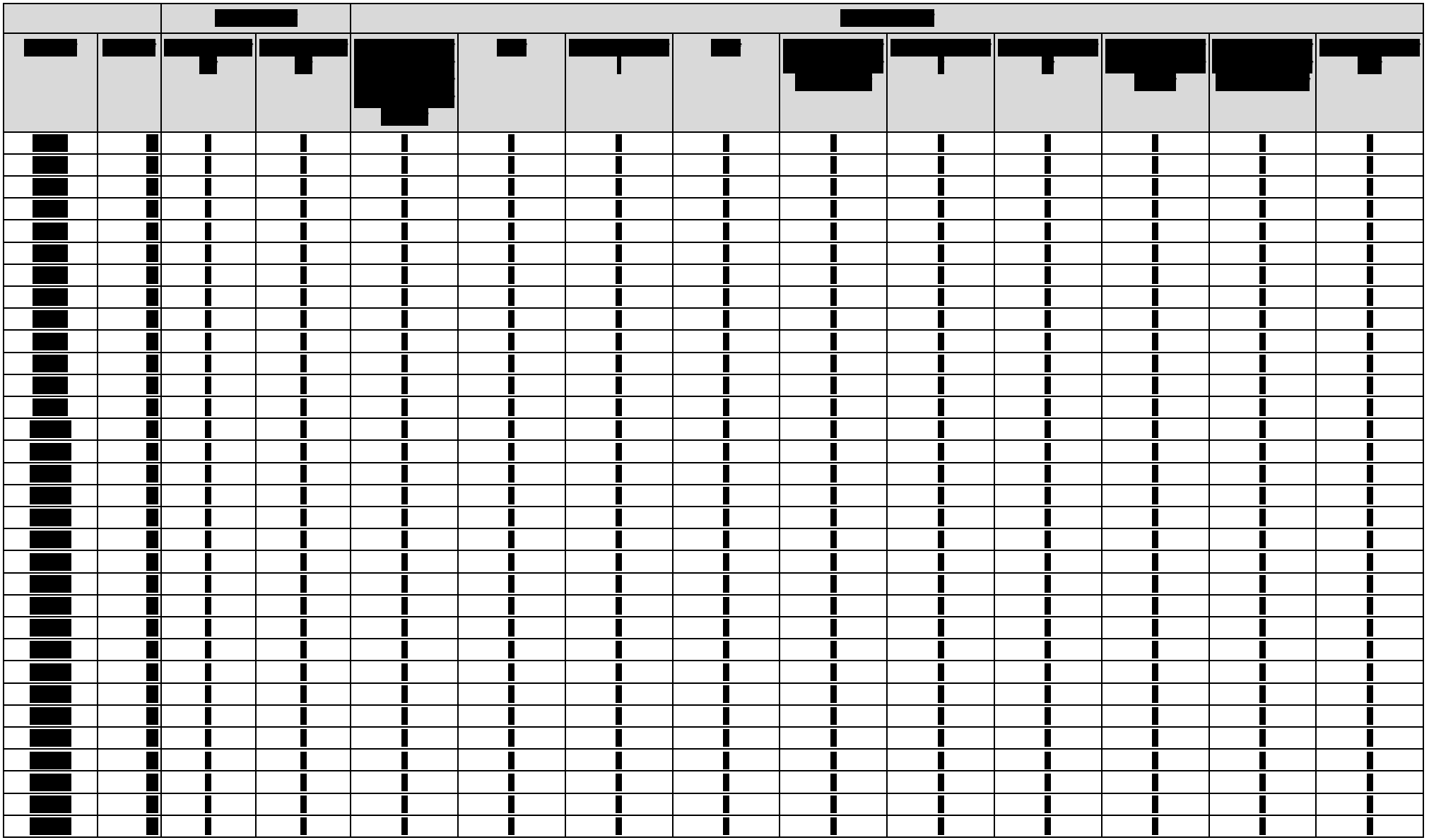

** Reason for censoring.*

[a] Dose interruption = dose interruption of >28 consecutive days (encorafenib or binimetinib) or 2 missed consecutive irinotecan, fluorouracil, or folinic acid or >4 missed consecutive cetuximab doses.

Table 10: TTD - Events and subjects censored by timepoint - (Safety set – FOLFIRI with cetuximab)

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** Reason for censoring.*
[a] Dose interruption = dose interruption of >28 consecutive days (encorafenib or binimetinib) or 2 missed consecutive irinotecan, fluorouracil, or folinic acid or >4 missed consecutive cetuximab doses.

Table 11: TTD - Events and subjects censored by timepoint - (Safety set – irinotecan with cetuximab)

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** Reason for censoring.*

[a] Dose interruption = dose interruption of >28 consecutive days (encorafenib or binimetinib) or 2 missed consecutive irinotecan, fluorouracil, or folinic acid or >4 missed consecutive cetuximab doses.

Table 12: TTD - Events and subjects censored by timepoint - (Safety set – Enco with cetuximab, 1 prior mCRC therapy)

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** Reason for censoring.*

[a] Dose interruption = dose interruption of >28 consecutive days (encorafenib or binimetinib) or 2 missed consecutive irinotecan, fluorouracil, or folinic acid or >4 missed consecutive cetuximab doses.

Table 13: TTD - Events and subjects censored by timepoint - (Safety set – Control, 1 prior mCRC therapy)

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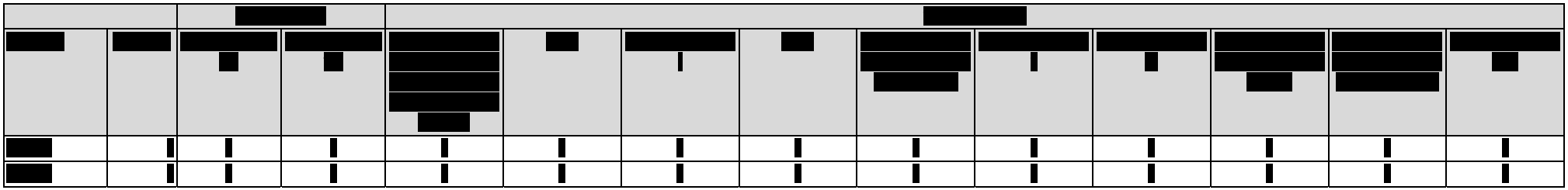

** Reason for censoring.*
[a] Dose interruption = dose interruption of >28 consecutive days (encorafenib or binimetinib) or 2 missed consecutive irinotecan, fluorouracil, or folinic acid or >4 missed consecutive cetuximab doses.

Table 14: TTD - Events and subjects censored by timepoint - (Safety set – FOLFIRI with cetuximab, 1 prior mCRC therapy)

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** Reason for censoring.*
[a] Dose interruption = dose interruption of >28 consecutive days (encorafenib or binimetinib) or 2 missed consecutive irinotecan, fluorouracil, or folinic acid or >4 missed consecutive cetuximab doses.

Table 15: TTD - events and subjects censored by timepoint - (Safety set – irinotecan with cetuximab, 1 prior mCRC therapy)

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** Reason for censoring.*

[a] Dose interruption = dose interruption of >28 consecutive days (encorafenib or binimetinib) or 2 missed consecutive irinotecan, fluorouracil, or folinic acid or >4 missed consecutive cetuximab doses.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Encorafenib in dual therapy with cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Issue 5 only

Further clarification questions

Pierre Fabre responses

April 2020

File name	*Version*	*Contains confidential information*	*Date*
ID1598 encorafenib ERG issue 5 further clarification questions	***1***	***Yes***	***8 April 2020*** ***(note, original response sent via email on April 1st)***

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.

Issue 5: **The ERG apologises for the late request, but would be grateful if the company could indicate how the model should be run to replicate the tornado diagrams of Figure 22 and Figure 23 of Document B.**

The tornado diagrams can be replicated from the cost effectiveness (excel) model as follows:

1. Select ‘results detailed’ tab
2. Ensure ‘pairwise + DSA’ is selected
3. Select ‘comparator selection’ (e.g. FOLFIRI or Lonsurf)
4. Select ‘run DSA’

NICE National Institute for Health and Care Excellence

Professional organisation submission

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]**and advanced sub group of the NCRI colorectal Studies Group, on behalf of the RCP.**

3. Job title or position	
4. Are you (please tick all that apply):	**X**☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	[redacted] **and advanced sub group of the NCRI colorectal Studies Group, on behalf of the RCP.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**NO**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	BRAF mutant colon cancer is a very rare sub type of colorectal cancer that's associated with a much worse survival than any other type. Despite advances in RAS wild type colon cancer we have seen very little shift in median survival for BRAF mutant cancer until the results of the BEACON study. We now eagerly await the results of the ANCHOR first line trial to see if the benefit is even larger in first line. This regimen is very well tolerated and I have treated trial patients from across Scotland. All say it is much easier than any SACT they have had previously and this is reflected in the quality of life data which was presented at ASCO GI 2020. There are two main aims in my mind with this treatment. Firstly to control difficult symptoms – patients with BRAF mutant cancer often have large primary tumours and more peritoneal disease – and

disability.)	secondly to prolong survival. The gain of 3+ months for a patient who has an expected survival of less than six months is vastly different proportionally to that of someone with a more indolent cancer. This group of patients respond to first line SACT but relapse very quickly and from our own audit data few manage conventional second line SACT. Our experience of this doublet and triplet from the trial though is that we see more prolonged disease stabilisation, a good quality of life, convenient scheduling (particularly if using two weekly cetuximab) and some very durable responses. In addition the data suggesting we may see the same efficacy but less cost and toxicity with the doublet is very helpful for patients and the health service alike.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improved quality of life Ability to have a small number of extra months to plan for end of life, particularly for those with young families. Reduction in disease bulk along for patients with peritoneal disease it can be difficult to put a figure of x percent on this.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Definitely. This is the largest unmet need I can see in colon cancer (apart from MSI high cancers and immunotherapy which I would regard as equally as important)
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	We would generally use FOLFIRI or alternatively lonsurf for these patients. For lonsurf its scheduling is easy but QOL is less good for patients and we rarely see disease shrinkage and rather stabilisation at best.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	I follow the WOSCAN guidelines, whereas colleagues in England would generally follow NICE guidance. It should be noted that Lonsurf is listed as the only NICE approved treatment option for patients with colorectal cancer after first line chemotherapy which reflects the need for new innovations in this disease area. https://pathways.nice.org.uk/pathways/colorectal-cancer#path=view%3A/pathways/colorectal-cancer/managing-metastatic-colorectal-cancer.xml&content=view-index There are similar guidelines elsewhere, although evidence base for treatment when the BRAFV600E mutation is limited, due to the lack of effective targeted treatment options until this point. Because this doublet is so much better tolerated and less toxic than standard chemotherapy we have applied for national approval for exceptional funding to use it in the COVID pandemic.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway is straight forward due to limited treatment options, as previously stated above. We would use this treatment either in a second or third line setting.
• What impact would the technology have on the current pathway of care?	If this technology was made available, it would become the standard of care for treatment of patients with the BRAFV600E mutation who have previously been treated with systemic therapy. This is the only treatment regimen to date that demonstrates both a clinically meaningful and statistically significant difference in terms of overall survival within this patient population within a phase 3 trial.
10. Will the technology be used (or is it already used) in the same way as current care	no

in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	No PICC lines, shorter day unit stay, less myelosuppression which is particularly important in the context of COVID.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Oncology departments that prescribe SACT
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Minimal extra training.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
• Do you expect the technology to increase length of life more than	yes

current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	no
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	This is easier for the reasons described above.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	no
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I don't think so. This was fairly well covered in the QOL data from the trial, although not sure how this reflects in the EQ-5D measurements that are using by NICE
16. Do you consider the technology to be innovative in its potential to make a	Yes, as described above

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, definitely, the first step change ever really in this disease – in terms of something that's easily administered and tolerated. There are some other small subgroups identified in more toxic four drug regimens but these would be less relevant to the general population of BRAF patients.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, this sub group of patients have the poorest survival of all colon cancer patients.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main issues for these patients are related to the side effects from their rapidly progressing metastatic cancers. The toxicity from the regimen itself is very manageable.
Sources of evidence	
18. Do the clinical trials on the	Yes; one could argue that FOLFIRI Cetuximab is not standard of care but I can see why it was felt

technology reflect current UK clinical practice?	necessary to have cetuximab in both arms and we do know from studies such as CRYSTAL that these patients do benefit from cetuximab but its just they benefit less than the wild type population. Lonsurf wasn't published at the time and certainly more patients received oxaliplatin based first line treatment so the comparator arm needed to be irinotecan based.
• If not, how could the results be extrapolated to the UK setting?	As above
• What, in your view, are the most important outcomes, and were they measured in the trials?	OS, PFS and QoL. – All were measured in the BEACON trial and demonstrated statistically significant benefits vs. comparator
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	no
19. Are you aware of any relevant evidence that might	No, although it should be noted that there is a paucity of comparative data within this population due to the

not be found by a systematic review of the trial evidence?	small patient numbers involved.
20. Are you aware of any new evidence for the comparator treatment(s) (if applicable) since the publication of NICE technology appraisal guidance?	NA
21. How do data on real-world experience compare with the trial data?	NA
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	NO
22b. Consider whether these issues are different from issues	

with current care and why.	

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • FIRST significant advance for this group of patients ever • They are a small sub group of patients who do extremely badly with standard of care options • The regimen is well tolerated • Efforts were made to collect QOL data which support this • The proportional gain for this particular group of patients who are approaching end of life is particularly important.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Thank you for agreeing to give us 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Naureen Starling**
2. Name of organisation	**The Royal Marsden**

3. Job title or position	**Consultant Medical Oncologist in Gastrointestinal Cancers**
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve survival, shrink tumours and improve symptoms for patients with metastatic colorectal cancer who comprise the 10% of patients whose tumours show the BRAF V600E mutation. This group of patients often have a distinct more aggressive tumour biology and poorer survival.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in progression free survival and overall survival with any degree of tumour shrinkage (but ideally a high proportion of patients with disease control i.e. complete response, partial response and stable disease). I would not cite a particular numerical increase in absolute survival gain (noting that months would be more meaningful than weeks) but I would note that in general a good hazard ratio (i.e. <0.7 (i.e. 30% relative reduction in death) would be something I would normally assess for any clinical trial of SACT in the palliative setting. If there is a reasonable proportion of patients with partial response (i.e. >30% shrinkage i.e. 1in 5) this would also be meaningful but I would tend to look at the waterfall plot to get a better sense of the proportion of patients having some degree of tumour shrinkage and duration of that response (i.e. duration of response for several months is clinically meaningful). If patients have symptoms due to tumour burden then early tumour shrinkage and prolonged disease control can reduce symptoms and improve quality of life.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is unequivocally an unmet need. BRAF V600E mutant advanced colorectal cancer (10% of patients with stage IV colorectal cancer) has been recognised as a distinct form of colorectal cancer for years and known to confer a more aggressive disease course and worse survival outcomes (although there is some emerging variability). Until recently we have not been able to target the BRAF mutation and personalise treatment for these patients with effective therapy and have been using chemotherapy including more toxic intensified chemotherapy regimens. An understanding of the biology of BRAF mutant advanced colorectal cancer has translated into an effective targeted therapy approach (EGFR and BRAF inhibitors combined)

	that specifically targets the mutation and primary resistance pathways, does not involve chemotherapy, has a more tolerable side effect profile (patients tell me that it is a much better experience than being on chemotherapy) is associated with durable tumour control (and rapid tumour shrinkage for patients who have shrinkage) and improves survival and patient well-being.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients with BRAF V600E mutated advanced colorectal cancer and currently treatment with chemotherapy. For instance for patients who are fit enough they may be offered triplet chemotherapy if they are treatment naïve (FOLFOXIRI) although bevacizumab cannot be given alongside this as this is not approved in the NHS in any line of treatment (in the TRIBE study the patients who had BRAF mutation had a doubling of their survival with FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab although small patient numbers). Otherwise they may have sequential combination chemotherapy i.e. FOLFOX or CAPOX first line followed by FOLFIRI 2nd line (or vice versa) and, if fit enough, trifluridine-tiparacil (Lonsurf) 3rd line. Some clinicians may consider the addition of an anti-EGFR antibody in the first line setting in combination with chemotherapy as per NICE guidance. Anti-EGFR antibodies are not approved in the 2nd line setting in the NHS.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are the ESMO guidelines (the 2018 pan-Asian ESMO guidelines are more up-to-date) and NICE guidelines (including technology appraisals permitting anti-EGFR antibodies in RAS wild type patients in the first line setting in combination with chemotherapy). The use of anti-EGFR antibodies in BRAF mutated colorectal cancer is variable
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The current pathway is well defined in terms of 1st, 2nd and 3rd line sequential chemotherapy options for advanced colorectal cancer. The technology under consideration would provide another treatment option and line which many clinicians (including myself) would offer to patients in the 2nd line setting so that they have a chance to benefit from the durable tumour shrinkage earlier in their treatment journey and with a chemotherapy-free, well tolerated

state if your experience is from outside England.)	treatment. It is my experience that patients who I have treated with this combination find it much easier to cope with than chemotherapy. Preservation of performance status and reduction in tumour burden also facilitates a further line of treatment with chemotherapy on progression. Again, in my experience there can be a high rate of attrition for treatment of patients with BRAF mutated colorectal cancer after 2nd line chemotherapy if there is disease progression, markedly increased disease burden and reduction in performance status. My impression from my experience is that this technology in the 2nd line preserves performance status since it is associated with tumour shrinkage and disease control, thereby facilitating further lines of treatment. In colorectal cancer in general there is evidence that effective sequential therapy is associated with better survival.
• What impact would the technology have on the current pathway of care?	It would provide an important, effective, life-extending well tolerated chemotherapy-free targeted drug treatment for the 10% of patients with BRAF V600E mutated advanced (incurable) colorectal cancer to be used in either the 2nd or 3rd line (preference is 2nd line and 2/3 of the patients in BEACON were treated in the 2nd line).
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As above, in place of current second or third line chemotherapy (many clinicians would want to offer this option second line to maximise chance of disease control earlier in the treatment pathway, noting that some patients may not be well enough for treatment if it is left until the 3rd line).
• How does healthcare resource use differ between the technology and current care?	If used in the second line the comparator would be FOLFIRI. EC would not require a PICC line/portacath (i.e. a central venous access device with a 10% risk of line-related complications), is a shorter iv infusion (less chair time) and does not require a 2 day infusional pump and disconnection (district nurse/return to medical day unit i.e. less human resource). EC does require some counselling regarding the oral medication use (but this might be in place of counselling regarding the post chemotherapy anti-emetics that would normally occur with FOLFIRI). The E component of EC would require some additional dispensing time in pharmacy.

	If used in the 3rd line the comparator would be trifluridine-tiparacil which is an oral treatment every 4 weeks. Here there would be additional resource needed for the intravenous component of EC i.e. chair and nurse time in the medical day unit.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In specialist oncology prescribing clinics in secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Cetuximab (intravenous anti -EGFR chimeric antibody) has been used in the NHS in colorectal cancer for many years since the pivotal BOND study published in NEJM in 2004 and GI oncologists are already very familiar with its administration as an intravenous drug every two weeks (usually over one hour). Medical day units will be very familiar with this drug and its infusion (a relatively short infusion with short chair time in comparison to most chemotherapy drugs with little in the way of pre-meds). Medical teams are very conversant with management of the limited side effects, most notably skin toxicity (with pre-emptive measures) so no additional training would be required. Encorafenib is an oral BRAF inhibitor already used in melanoma and hospital formularies and pharmacies will be familiar with its dispensing, dosing and counselling. Oncologists are mostly familiar with the side effects of BRAF inhibitors but training would be needed to ensure CNSs and the medical team were up to speed to consent and counsel patients appropriately with regard to the specific combination of EC. In my centre, for instance, we conducted teaching sessions to the inter-disciplinary team (doctors, nurses, pharmacists) as we accessed EC compassionately.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – as stated above: - Good chance of tumour shrinkage and disease control (i.e. if there are symptoms, a reduction in symptoms) – often seen early on within the first 6-8 weeks - Good side effect profile which is distinct from chemotherapy (patients have told me it's completely different to being on chemotherapy with some saying they "got their life back" - More convenient for patients – less time in the medical day unit with one intravenous drug and then tablets to take at home

• Do you expect the technology to increase length of life more than current care?	Yes- as stated above and based on the BEACON trial. I would also postulate that as more patients access this treatment, we will see more patients well enough to have further lines of treatment (including the chemotherapy that this technology displaces) which I think will also impact on and extend survival for this group of patients with BRAF mutated colorectal cancer (1 in 10 patients) who have hitherto had worse survival than non-BRAF V600E mutated colorectal cancer.
• Do you expect the technology to increase health-related quality of life more than current care?	Anecdotally I have heard from patients that the experience of being on EC targeted treatment is different and better than being on chemotherapy so I would expect quality of life indices to be better (although I realise that the formal QOL scoring do not always capture some of the PROM/PREM aspects of treatments).
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology is specifically for patients with BRAF V600E mutated colorectal cancer i.e. not appropriate for the 90% of non-V600E mutated colorectal cancer.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical	The technology is easier to use than the current second line treatment (FOLFIRI) as there is less intravenous medication (i.e. one short iv infusions as opposed to two iv drugs, one of which must be given via a pump over 2 days) and EC does not require the patient to have an indwelling central vascular access device with associated discomfort, infection risk and thrombosis risk. EC also does not require three days of post treatment steroids with the associated risks that steroids pose (insomnia, raised blood sugars,

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.)	infection, behaviour changes). FOLFIRI is also associated with some specific side effects including hair loss, myelosuppression, diarrhoea, abdominal cramps, fatigue, altered taste and others. The psychological impact of hair loss should not be under-estimated (for both women and men). The main side effect to manage with EC is skin rash which will require some supportive medications to reduce skin dryness and risk of skin infections. Some patients may also experience joint aches and pains. The technology is slightly more involved if used in lieu of 3rd line trifluiridine/tiparacil as there is one intravenous drug as opposed to the total oral therapy of trifluridine-tiparacil. However, the treatment has a higher chance of tumour shrinkage than trifuridine-tiparacil (1 in 5 patients as opposed to 1 in 1 in 20 patients) and importantly has a much lower chance of fatigue and neutropenia – the latter is a common problem with trifuridine-tiparacil and fatigue can be difficult to manage. Of note, it is preferable to offer EC to patients with pre-treated BRAF V600 mutated advanced colorectal cancer in the Covid 19 pandemic as the risks of immune suppression are far less than with chemotherapy (either FOLFIRI or trifluridine-tiparacil).
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We would offer EC to patients with evidence of progressive (growing) cancer of their scan after first-line (or 2nd line) chemotherapy. We would stop EC if there was evidence of emerging resistance (i.e. patient's symptoms are increasing, tumour markers are increasing and the CT scan shows tumour growth).

	There is no additional testing (CT scans are standard of care).
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	As mentioned, patients I have treated comment on the marked difference in the experience of EC as compared to previous chemotherapy treatment(s) they have had. I am not sure to what extent the current QALY measures can capture this important patient reported experience measure (PREM) and intra-patient comparison of chemotherapy versus non-chemotherapy-based treatment centred on their own experience. Some have noted that they are more able to work or conduct the other activities they would like to be involved in (i.e. going to the gym/exercising) and continue to have a social life (as opposed to the treatment and, importantly, side effects dictating what they can do and when).
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes as stated above. Innovative drug treatment exploiting specific biology of a sub-group of patients with advanced colorectal cancer (1 in 10), chemotherapy-free, effective, well tolerated treatment as compared to the current chemotherapy based option with associated logistical considerations (including central venous access devices), side effects (fatigue, diarrhoea, abdominal discomfort, myelosuppression, hair loss) and supportive medications which include steroids.
• Is the technology a 'step-change' in the management of the condition?	I firmly believe that it is.

• Does the use of the technology address any particular unmet need of the patient population?	Yes – an effective treatment specifically targeted to the BRAF V600E mutated colorectal cancer – a sub-group of colorectal cancer with a worse outlook and previously no individualised treatment approach.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Please see my answers to Q14 and Q16 above which cover this response.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	The comparator in the UK would be FOLFIRI and not FOLFIRI plus cetuximab or irinotecan plus cetuximab in the second line setting. For the third line it would be trifluridine-tiparacil. Cetuximab is not NICE approved for 2nd line use in the NHS (there is a trial of chemo +/- anti EGFR antibody – study 181 which provides the evidence for anti-EGFR antibodies 2nd line). It is restricted only to the first-line setting.
• If not, how could the results be extrapolated to the UK setting?	The effect of the addition of anti-EGFR antibodies in the second line in BRAF mutated cancers could be modelled versus FOLFIRI alone. There is a meta-analysis showing the effect of anti-EGFR antibodies in BRAF mutated colorectal cancer showing a small benefit (another meta-analysis suggesting no benefit).

• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, progression free survival and response rates (to include complete response, partial response and stable disease with note made of the shape of the waterfall plot for response data and duration of response)
• 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?	Not in my experience to date.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology	No

appraisal guidance [TA118/ TA112/ TA242/ TA307]?	
22. How do data on real-world experience compare with the trial data?	We published our single centre real world experience a few years ago (before FOLFOXIRI and EC were treatment options): "Treatment and Survival Outcome of BRAF-Mutated Metastatic Colorectal Cancer: A Retrospective Matched Case-Control Study. Kayhanian H, Goode E, Sclafani F, Ang JE, Gerlinger M, Gonzalez de Castro D, Shepherd S, Peckitt C, Rao S, Watkins D, Chau I, Cunningham D, Starling N. Clin Colorectal Cancer. 2018 Mar;17(1):e69-e76. doi: 10.1016/j.clcc.2017.10.006." All colorectal cancer patients tested for BRAF mutation, from October 2010 to November 2014 were identified. 43 of 503 patients (8.5%) tested had BRAF-MT mCRC and were compared with 88 BRAF-WT controls. Median overall survival (mOS) was 18.2 months for BRAF-MT and 41.1 months for BRAF-WT mCRC patients (hazard ratio, 2.74; 95% confidence interval, 1.60-4.70; P < .001). Progression-free survival for BRAF-MT and WT patients, respectively, was: 8.1 months versus 9.2 months (P = .571) first-line, 5.5 months versus 8.3 months (P = .074) second-line, and 1.8 months versus 5.6 months (P = .074) third-line. Treatment using sequential fluoropyrimidine-based doublet chemotherapy was similar between both groups. Anti-epidermal growth factor receptor (EGFR) therapy was mainly given third-line with progressive disease in 90% (n = 9 of 10) of BRAF-MT patients at first restaging.

	Scans in standard care were undertaken every 12 weeks so PFS is likely to be over-estimated. In addition the numbers are small. Since this was undertaken our tertiary high-volume centre has identified many more BRAF MT patients and we are planning to extend this real world series.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	I am not aware of any.
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	

24. Before taking encorafenib, patients must have mCRC with BRAF V600E mutation confirmed by a validated test. Is V600E mutation testing part of routine clinical practice in the NHS? Who receives V600E testing in practice?	Yes – it has been for some years. From this year (2020) the NHS test directory for genomics England will also mandated that where gene testing is part of standard of care (BRAF V600E is listed for advanced colorectal cancer on the test directory) then that will be undertaken on an NGS capture based panel. All patients with advanced colorectal cancer should be tested for RAS and BRAFV600E when they are first diagnosed with advanced disease (i.e. we would identify early anyone who might be a suitable candidate for cetuximab/encorafenib ideally in the 2nd line).
25. The company's indirect treatment comparison is based on key assumptions of equivalence between: • cetuximab and panitumumab • FOLFIRI and single agent irinotecan Is cetuximab considered to be equivalent in clinical efficacy to	Cetuximab and panitumumab have never been compared head to head (nor are ever likely to be) but are considered equally effective. FOLFIRI and irinotecan monotherapy have not been compared head to head in a large randomised study but are considered to be of similar efficacy with FOLFIRI being well tolerated. In my experience, when I used single agent irinotecan (early 2000's) there were more dose delays and dose reductions as compared to my experience with FOLFIRI.

panitumumab? Is FOLFIRI clinically equivalent to single agent irinotecan?	
26. Is single agent irinotecan considered to be established clinical practice in the NHS for treating metastatic colorectal cancer? Is it a relevant comparator for encorafenib?	Not in 2020. When irinotecan was first introduced in the late 1990's it was at a 350 mg/m2 three weekly dose (and was better than best supportive care according to the clinical trial that had reported at the time). At this dose and schedule, it was associated with many toxicities (myelosuppression, fatigue, mucositis). In contract when combined with infusional 5FU every 2 weeks (180 mg/m2 dose) in the regimen FOLFIRI it is far more tolerable. FOLFIRI is commonly used in either the 1st or 2nd line treatment of advanced colorectal cancer.
27. When is encorafenib likely to be used in the clinical pathway? Is best supportive care as a relevant comparator at this point in the pathway?	Encorafenib would not be used on its own in the clinical pathway for BRAF V600E MT colorectal cancer (it does not have single agent activity). It would be with cetuximab (based on pre-clinical models the two must be used together to dampen the feedback loop that BRAF inhibition alone would otherwise activate).
28. The company position ecorafenib with cetuximab 2nd line:	I agree this is appropriate in UK clinical practice. This follows our pathway i.e. 1st line FOLFOXIRI -> 2nd line trifluridine-tiparacil 1st line FOLFOX/CAPOX ->2nd line FOLFIRI ->3rd line trifluridine-tiparacil

• as an alternative option to FOLFIRI (in patients previously treated with FOLFOX at first-line) or • as an alternative option to trifluridine-tipiracil (in patients previously treated with FOLFIRI at second-line) or • as an alternative option to trifluridine-tipiracil (in patients previously treated with FOLFOXIRI at first-line). Is this appropriate?	
29. What dosing is used in practice for cetuximab for metastatic colorectal cancer,	We use the dosing and schedule as per the CDF (as we must follow the CDF rules).

the following information is given in the company submission (CS doc b p12): "Cetuximab: • The SmPC recommendation on dosing is an initial dose of 400 mg per m2 body surface area, followed by 250 mg/m2 for all subsequent doses given once weekly. • In contrast, CDF guidance from NHS England, which reflects current clinical practice in England, recommends a maintenance dosing	

schedule of 500 mg/m2 given every 2 weeks”	

Key messages

30. In up to 5 bullet points, please summarise the key messages of your statement.

- Step-change innovation for the 1 in 10 patients with advanced bowel cancer harbouring the BRAF V600E mutation
- Extends survival, causes good and durable tumour shrinkage and is well tolerated with a side effect profile distinct from chemotherapy
- An important **chemotherapy-free targeted drug combination** i.e. a kinder, smarter treatment than current therapies
- The single biggest innovation for this sub-group of colorectal cancer since the V600E mutant group was first identified
- Increasing the potential treatment lines for this group of patients is also likely to improve survival for this groups of patients

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.

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Your privacy

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Thank you for agreeing to give us 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 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 13 pages.

About you	
1. Your name	**Harpreet S Wasan**
2. Name of organisation	**Hammersmith Hospital, Imperial college healthcare NHS trust**

3. Job title or position	**Consultant & Reader in (Medical) Oncology** **Lead for Medical oncology &** **Clinical Divisional NIHR Lead for Cancer for N.W London Research network**
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 this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1) To improve overall survival, induce significant and durable responses and prolong life, with a preserved quality in the BRAFV600E subset of metastatic colorectal cancer (mCRC), after progressing on one or two lines of prior therapy, which hitherto had no international consensus as to what was the best treatment approach. 2) To specifically demonstrate BRAF-targeted treatment effectiveness in BRAFV600E mCRC, without any cytotoxic chemotherapy in the treatment regimen.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In this poor prognosis mCRC subset which is at the worse-end of the response and survival spectrum of all mCRC patients, durable disease control (CR+PR+SD) is considered clinically significant as historically this was very difficult to achieve with any conventional chemotherapy regimen. This is even more important after 1st line progression as dissemination is rapid and usually very symptomatic and the pattern of disease in BRAFV600E cancers is both more atypical (e.g. peritoneal and bone metastases). It is very unusual to see responses to help symptoms in this context with conventional treatments. Thus, any degree of slowing the tumour down, stabilisation and reduction would be clinically significant
9. In your view, is there an unmet need for patients and healthcare professionals in this	Yes, as summarised in 8 – unmet need as rapid symptomatic progression and death – with less BRAFV600E patients being fit for 2nd or 3rd line treatments, with poor symptom control and more disability. There are healthcare professionals who would not consider 2nd line treatments worthwhile due to their poor outcomes, and increased toxicity historically

condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	After failure of first line (combinations with Doublets and triplets) cytotoxic chemotherapy, there are no clear effective options specifically beneficial in BRAFV600E mCRC. EGFRi inhibitors are not available in 2nd or 3rd line in the NHS. Trifluridine-Tipiracil is not particularly effective in the majority of mCRC and although no differences in OS and PFS were observed between wild-type *BRAF* and *BRAF*-mutated tumours in the studies, no definitive conclusions can be made due to the small sample size and their is no logical scientific reason why BRAFV600E should be more sensitive to Trifluridine-Tipiracil.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	mcRC : in the UK- network guidelines are every similar across networks 2016 ESMO guidelines where biological can be used 1st-3rd line, similarly NCCN guidelines For the BRAFV600E subset there is controversy to the role of both EGFRi and VEGFi drugs and most of Europe and US will use at least three if not 4 drugs (FOLFOXIRI-Bev) in BRAFV600E mutants as the disease is so aggressive with poorer outcomes – (so " a throw the kitchen sink" attitude as emerged to this nasty subtype.)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is	in the UK- network guidelines are every similar across networks and there is universal agreement that BRAFV600E mCRC do very badly – hence why clinical trials with newer targeted options are the favoured approach My Experience is Global including US and Europe (I am on the CRC guidelines ESMO committee and also involved in many CRC trials being set up in the US including on the steering and development committee of BEACON and BRAFV600E studies first line.

from outside England.)	
• What impact would the technology have on the current pathway of care?	It would offer for the first time in CRC (not withstanding the recent NHSE and NICE CoviD19 MSI – immunotherapy mCRC guidance witch was unexpected and due to extraordinary circumstances) a proven treatment in the BRAFV600E subset that clearly prolonged OS, PFS and RR without debate.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be novel and not currently used – and will be used as in the BEACON Trial setting
• How does healthcare resource use differ between the technology and current care?	The BEACON regimen is effective in OS, PFS and RR in the 2nd/3rd line setting whereas hitherto the treatments were unclear benefit. The healthcare resource use is lower with The BEACON regimen with oral therapy and shorter chemotherapy visits (day-care) times then conventional chemotherapy (allowing more capacity overall) – less toxicity admission rates and QOL preservation requiring less allied healthcare input
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care & specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training for toxicity management already embedded in the NHS with experience of cetuximab skin toxicity and BRAFV600E inhibitors already used extensively in cancer centres in Melanoma. Testing for BRAFV600E is routine already within the RAS testing platforms in the majority of the country and the genome hubs will further standardise this also.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, as current 2nd line+, therapies in this context of BRAFV600E mCRC are invariably ineffective and toxic Disease control rate can be achieved in ~ ¾ of patients compared with less than 1/3 historically Up to 5% complete response rate which is exceptional for any solid tumours, and conventionally this is never seen otherwise
• Do you expect the technology to increase length of life more than current care?	Yes, significant increase (HR0.6) in OS
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as ineffective chemotherapy is detrimental and this has been demonstrated in the BEACON study. Up to 5% complete response rate means exceptional benefit in these patients also.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I envisage It should be equally beneficial across the patient spectrum that is being currently offered 2ndIIne+ Cytotoxic chemotherapy and may even, as better tolerated, give more patients the option and chance of a treatment, especially the elderly. Patients with high burden of disease and more symptomatic are likely to get relatively more benefit in terms of QOL and symptom response.
The use of the technology	
14. Will the technology be	Easier - The BEACON regimen healthcare resource use is lower with The BEACON regimen with oral

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.)	therapy and shorter chemotherapy visits (day-care) times then conventional chemotherapy (allowing more capacity overall) – less toxicity admission rates and QOL preservation requiring less allied healthcare input. Conventional chemotherapy treatments FOLFOX and FOLFIRI require CVADs/ Ports insertion as an extra procedure and regular line-care for these indwelling lines and dealing with their complications, takes up much time for chemotherapy units impinging on resource and capacity Grade 3/4 adverse event (AE) and Any serious AE in the trials was higher with conventional treatments than the new treatment option – so there will be a knock on costs and time in managing this via primary and hospital care usage.
15. Will any rules (informal or formal) be used to start or stop	Conventional parameters would apply – when not benefiting (CT disease progression), unacceptable

treatment with the technology? Do these include any additional testing?	toxicity or patient choice.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The 5% complete response rate (and those in addition that get a high quality response – shrinkage) means exceptional benefit in these patients which could lead to a tail of patients who would be able to have curative secondary interventions e.g. liver or lung surgery or ablation or SABR for residual oligo-metastases. Grade 3/4 adverse event (AE) and Any serious AE in the trials was higher with conventional treatments than the new treatment option – so there will be a knock on costs and time in managing this via primary and hospital care usage. The new technology is also potentially less immunosuppressive than conventional cytotoxics – which may have benefits in the C19 era
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – as no conventional cytotoxic untargeted chemotherapy is needed and one is targeting the causative BRAFV600E mutation pathway directly and its feed back loop in a very specific way. This is the aspiration of all oncology drug development currently.
• Is the technology a 'step-	In my view no question that this is the case – Only BRAFV600E biomarker testing and treatment affecting

change' in the management of the condition?	up to 10% of mCRC and MSI- H / dMMR mCRC patients (3-4%) fall into this category for CRC currently. So the BRAFV600E approach will help more patients proportionally than immunotherapy.
• Does the use of the technology address any particular unmet need of the patient population?	In this poor prognosis mCRC subset disease control historically was very difficult to achieve with any conventional chemotherapy regimen. This is even more important after 1st line progression as dissemination is rapid and usually very symptomatic It is very unusual to see responses to help symptoms in this context with conventional treatments. Thus, any degree of slowing the tumour down, stabilisation and reduction would be clinically beneficial. The unmet need is rapid symptomatic progression and death – with less BRAFV600E patients being fit for 2nd or 3rd line treatments, with poor symptom control and more disability. There are healthcare professionals who would not consider 2nd line treatments worthwhile due to their poor outcomes, and increased toxicity historically
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Overall, Grade 3/4 adverse event (AE) and all serious AE's in the trials was higher with conventional treatments than the new treatment option – so there will be a knock on costs and time in managing these via primary and hospital care usage. (as well as QOL) The Training for specific toxicity management of the new technology are already embedded in the NHS with experience of cetuximab skin toxicity and BRAFV600E inhibitors already used extensively in cancer centres in Melanoma. In the Trials these toxicities were manageable and rarely a reason for discontinuation
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	OS, PFS, DCR / RR , SAE's and QOL – all measured in a randomised prospective fashion with accepted conventional trials methodology
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	These analyses e.g. CEA response are on-going and incomplete as yet – no surrogates used in primary endpoints.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of this.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am not aware of this.
21. Are you aware of any new evidence for the comparator	I am not aware of this.

treatment(s) since the publication of NICE technology appraisal guidance [TA118/ TA112/ TA242/ TA307]?	
22. How do data on real-world experience compare with the trial data?	This is only just starting with expanded access programmes globally – there is no clear reason why real-world experience should not be comparable.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware although BRAFV600E occurs more commonly in women Cf Men
23b. Consider whether these issues are different from issues with current care and why.	No real differences than already stated above
Topic-specific questions	

24. Before taking encorafenib, patients must have mCRC with BRAF V600E mutation confirmed by a validated test. Is V600E mutation testing part of routine clinical practice in the NHS? Who receives V600E testing in practice?	Testing for BRAFV600E is a routine already within the RAS testing platforms in the majority of the UK and the genome hubs will further standardise this also in the few centres not using a combined RAS/RAF platform. BRAFV600E was a known adverse prognostic factor for many years so was tested before specific treatments were available and also embedded/ expertise via melanoma testing before CRC.
25. The company's indirect treatment comparison is based on key assumptions of equivalence between: • cetuximab and panitumumab • FOLFIRI and single agent irinotecan Is cetuximab considered to be equivalent in clinical efficacy to	Cetuximab is considered equivalent in clinical efficacy to panitumumab in all lines (1st to 3rd) and whther monotherapy or combination use FOLFIRI is clinically equivalent to single agent irinotecan in efficacy, but the latter has been largely dropped in the last 10 years -due to higher significant toxicity of 3-weekly single agent irinotecan compared to 2-weekly FOLFIRI. N.B BOTH were still allowed as an investigator choice, in the control arm of the trial highlighting their equivalence

panitumumab? Is FOLFIRI clinically equivalent to single agent irinotecan?	
26. Is single agent irinotecan considered to be established clinical practice in the NHS for treating metastatic colorectal cancer? Is it a relevant comparator for encorafenib?	FOLFIRI is clinically equivalent to single agent irinotecan in efficacy, but the latter has been largely dropped in the last 10 years -due to higher significant toxicity & lower safety of 3-weekly single agent irinotecan compared to 2-weekly FOLFIRI. (N.B BOTH were still allowed as an investigator choice, in the control arm of the trial highlighting their equivalence) The comparator is thus FOLFIRI in real terms as by far the most commonly used and is relevant as the control arm in reality as the commonest 2nd line regimen used in the UK.
27. When is encorafenib likely to be used in the clinical pathway? Is best supportive care as a relevant comparator at this point in the pathway?	(I assume encorafenib means this + cetuximab) – it will be used as in the trial context of 2nd / 3rd line after failure of at least one line of conventional therapy BSC unlikely relevant for 2nd line and 3rd line Trifluridine-Tipiracil is used currently on CDF.
28. The company position encorafenib with cetuximab 2nd line: • as an alternative option	YES for UK

to FOLFIRI (in patients previously treated with FOLFOX at first-line) or • as an alternative option to trifluridine-tipiracil (in patients previously treated with FOLFIRI at second-line) or • as an alternative option to trifluridine-tipiracil (in patients previously treated with FOLFOXIRI at first-line). Is this appropriate?	Although globally 2nd line FOLFIRI + cetuximab/ panitumumab Or FOLFIRI+ Ramicirumab Or FOLFIRI+ Aflibercept or FOLFIRI+ Bevacizumab would be used 2nd line – but these options are not funded in the UK Yes as currently UK 3rd line CDF - If patients have been exposed to all three cytotoxics prior:- I.e. FOLFOXIRI first line Or FOLFOX first line and then FOLFIRI second-line Or the reverse FOLFIRI first line and then FOLFOX second-line
29. What dosing is used in	400 mg per m2 body surface area, followed by 250 mg/m2 for all subsequent doses given once weekly is

practice for cetuximab for metastatic colorectal cancer, the following information is given in the company submission (CS doc b p12): "Cetuximab: • The SmPC recommendation on dosing is an initial dose of 400 mg per m2 body surface area, followed by 250 mg/m2 for all subsequent doses given once weekly. • In contrast, CDF guidance from NHS England, which reflects current clinical practice in England,	the label but in practice worldwide everyone uses maintenance dosing schedule of 500 mg/m2 given every 2 weeks The Covid19 situation has also led to a pragmatic company guidance in April 2020 of using 500 mg/m2 given every 2 weeks with encorafenib and endorsed by the US FDA

recommends a maintenance dosing schedule of 500 mg/m2 given every 2 weeks”	

Key messages

30. In up to 5 bullet points, please summarise the key messages of your statement.

- First ever targeted treatment (BRAFV600E), without cytotoxics in mCRC with level 1 evidence
- BRAFV600E is a poor prognostic and predictive factor with no treatment options with level 1 evidence historically
- BRAFV600E mCRC is at the devastating- end of the spectrum for CRC
- Well tolerated, with clinically meaningful patient benefits
- Very high complete response rates historically rare, reflecting its innovative and targeted role

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.

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Your privacy

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NICE National Institute for Health and Care Excellence

Patient expert statement

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Thank you for agreeing to give us your 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.

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 intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Deborah James**

2. Are you (please tick all that apply):	☐ **a patient with the condition?** ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Bowel Cancer UK The Royal Marsden
4. Did your nominating organisation submit a submission?	☐ **yes, they did** ☐ no, they didn't ☐ I don't know
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.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **I have personal experience of the condition** ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I live with Cancer. I use the word "Live" very much on purpose. I have Stage 4 BRAF – Diagnosed in 2016. I'm fully aware of the outcomes on average of metastatic BRAF colon cancer case studies. I'm aware I've already outlived my prognosis. This in itself comes with both mental and physical challenges. The challenges of not knowing if you are living or dying. You are only as good as your last scan. And yes along the way I've said goodbye to far too many people. As such I'm incredibly thankful to still be living and responding to treatment. I knew of this triplet early on in my diagnosis and tracked the research trials for it. I also knew that data was looking positive and that I could gain hope from it.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Bowel Cancer screening right now is not meeting expectations outlined by the government or by patient need. It was agreed to lower the screening in England from 60 to 50 two years ago and this has still not happened. The capacity crisis – mainly colonoscopy level is real, and Covid has only made it worse.ther is no solution being offered. Young people. – like myself are diagnosed too late in the system. There is limited awareness that bowel cancer isn't just an older, overweight bloke issue. As a result those under 50 are diagnosed at a later stage on average. This is simply not good enough. Once in the system – treatment for Stage 1-3 Bowel cancer seems standard across the board. However there has been little movement in the drugs used for many years. The addition of some targeted therapies give more options but there are limitations over their use. "Oxy" – from a patient perspective is harsh. 21 cycles and 2 years later I still have neuropathic damage. Stage 4 options seem very dependant union the trust you are in and the oncologist care received. From others I've spoken to – too many stories of people being told, well you have 1 too many lung tumours so "off you go" with lonsurf. Only to get second opinions and be around years later. I am treated as a private patient at a leading hospital. As a result I'm still alive 3.5 years later and am currently disease free – from 15 tumours including some in in-operable areas.
10. Is there an unmet need for patients with this condition?	Yes- 100% - we are 10 years (in my opinion) behind where breast cancer is in this country. As the 2nd largest cancer killer, more needs and must be done for Bowel Cancer. It's high on the NHS cancer strategy – and yet very little is actually changing. Right now, wait lists for diagnosis is increasing, and survival has hardly improved in the last 5 years. Its not Good enough.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The triplet has given me life and allowed me to reach a place medically I never thought possible. Even recently my last scan showed a full metabolic response to my treatment, no active disease and shrinking of all sites. Upon this meeting - Ive been on the triplet for exactly a year. Response was quick – we could see tumour markers falling almost immediately and response was shown on scans after only 6 weeks. I'm also on a very reduced dose of cetuximab (due to skin issues). We are looking to increase this. But it

	means that if patients do response they may be very sensitive to this pathway initially. Do you actually want technology feedback here? If so - SABR must be rolled out sooner (the funding model for radiotherapy is ridiculous). This technology has rendered my in-operable tumours dead. NGS should be standard. Personalisation is key. My cancer is my cancer. I need a flexible unique pathway to keep me alive – so do others.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Side effects. Whilst much less than chemo regimes we do need to know understand more about them when used on a larger scale. Change of Bowel Habits, Eye changes, Skin rashes and Tiredness are for me the key ones. Eyes: There is a transient change of eyes upon initial use of Bini. On the grape vine this has been reported to me by other patients but wasn't reported in the same way in clinical data. For me it was 6 hours after the first use. Transient loss of central vision and colour distortion and light sensitivity. This improved within 12 hours. After 4 days use it went away. I'm on a reduced dose of bini now – 66%. My eyes are very light sensitive, they get sore and dry. But regular eye tests show there are no structural changes to my eyes. It's something that must in my opinion be monitored frequently with those on these drugs. After a week break the same eye issues occurred upon the first dose. However I did note – that after a short break off bini third time– I suggested a graduated return. This build up actually worked and meant I didn't get the usual transient eye issues. Perhaps a strategy to note? Tiredness has no pattern. Exercise helps. I find my legs will get tired more easily after a run, but I think this may be to do with other things. Skin: I'm incredibly sensitive to skin changes and I'm not sure I'm representative of a regular person on cetuximab. It's improved over time. I was taking a daily antibiotic, however I learnt recently that it does nothing to improve my skin.i stopped taking it and my skin has actually improved! For me sunlight helps. This is unusual as a lot of people say it makes it worse. But evening sunlight is a medicine to it. Others have found anti histamine effective for the itching – it makes me too sleepy to take, but I'm sure it would work!

	Bowel Habbits This is utterly varied. Between urgent rushing and passing motions to consitpation. I believe its related in part to Enco – my bowels change 6 hours after taking it. Each patients must find the pattern and therefore the best time to take these. I choose midnight as I often feel quite sick after them – so by doing it this way you sleep if off! I know others who routinely take anti sickness with the enco – there are certainly waves of sickness. But there must be flexibility in the timings of the day to work with the patients meal and body (obviously with the 24 hour spacing) but don't be prescriptive saying "take in the morning". Overall however – these side effective are well tolerated and on the whole I have a good quality of life. I manage to run (very slowly I should add!) 5km a day and I work full time. Training and up-skilling of staff and capacity to deliver. Investment must be made. No point in having the equipment if no one knows how to use it. Education is key.
Patient population	
13. 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.	BRAF positive. I also suggest using sooner rather than last line. Change patient thinking that clinical trials are last resorts. We know outcomes are better when used in healthier patients with less previous lines. So give people hope earlier! I also suggest using NGS to track and monitor the tumour changing. Possibly allowing the rotation of targeted to chemo (some patients are showing good results with this approach). With the doublet / Triplet debate – I believe that one of the reasons I have responded so well to this is because I also have a GNAS mutation – along the MEK pathway – for which bini targets. I'm hesitant to remove bini because I think this is giving the added response. I think NICE should think carefully

	before dismissing the triplet for ALL patients. If oncologists believe their may be a clinical benefit in the MEK pathway target then there should be the option to administer.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**The slowness of how quickly this will be rolled out – its needs to happen NOW. I got this a year ago. I'm very thankful for this. But others have died waiting. Others have had to educate their oncologists on this option. Some don't even know if they are BRAF as testing wasn't routinely done until their cancer progressed further.** Patients may need a break from time to time off treatment to allow skin or side effects to settle. They may also need to come back to this treatment as a later line as a re-challenge. Funding and approval for their use should not hinder this.
Other issues	
15. Are there any other issues that you would like the committee to consider?	Also the administration of cetuximab needs to be considered for two weekly effectiveness. Mainly due to quality of life, vs weekly hospital visits.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • This combination of drugs have kept me alive for the last year. Without them I wouldn't be here • The side effects are manageable with education but more knowledge on best ways to manage them must be obtained whilst in use. • The roll out of these drugs must happen quickly before more people die waiting for them	

- Educating the oncology field on their use and availability is key
- Ensure NGS of tumours alongside the use of the triplet to allow for future management of resistance.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Thank you for agreeing to give us your 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.

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 intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Alexander Mungo Graham Salkeld**

2. Are you (please tick all that apply):	**y**☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	The Royal Marsden
4. Did your nominating organisation submit a submission?	☐**y** yes, they did ☐ no, they didn't ☐ I don't know
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)	☐ **y** 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.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **y** I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I am 43. I have 3 children under 10 and moved away from London 3 years ago. Cancer has destroyed my life, my profession and myself. Each day is unique and takes is own blend of positivity and motivation. Anything I can do to improve that day is a blessing and this treatment did that.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	As a patient, I feel that the NHS have a very tough protocol to follow. Having eligibility to the Beacon trial triplet course is an example of the excellent work the NHS are able to do and convert someone's life through treatment during their cancer. By comparison, traditional chemotherapy treatments are a lot blunter and effect the surrounding world of the patient more so due to side effects. (without judging their efficacy)
10. Is there an unmet need for patients with this condition?	Yes – without doubt. There is the question of eligibility, but otherwise I felt it had a very good effect on me.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	It seems to be a lot more exact, precise, targeted than others. Whilst chemotherapy feels like it effects every part of your being, both your physical body and your mental body, The triplet was very different. My appearance was a lot better (less rashes and painful skin) but I did not feel poisoned all the time so exercise was easier. Also lethargy levels were a lot lower by comparison.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The only one I can think of is the efficacy of the Bevacizumab which was a rather convoluted process whilst in the RMH. Otherwise, its side effects were less 'raw' and made one feel a lot more human.
Patient population	
13. Are there any groups of patients who might benefit	I believe anyone who wants or needs to live an active life. I have three children under the age of 10 so energy is something I miss, now under Folfori. I would expect this to be more targeted at younger

more or less from the technology than others? If so, please describe them and explain why.	patients for that reason. The real answer is that it should be accessible to everyone who is eligible and in need of it
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not that I am aware of - cancer being blind?!
Other issues	
15. Are there any other issues that you would like the committee to consider?	I would like the committee to consider the severity of the alternatives that are patient available and their own ramifications that aren't as amplified under this treatment. This gave me a much-improved quality of life with is invaluable and let me see past my cancer. After 11 treatment of Folfori, I know and feel the difference every day. This combination improved patient quality of life and wellbeing without questions.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • Improvement of quality of life • Less intrusive that other cancer treatments	

- I feel like a vast improvement medically, to be able to single out and target a specific cancer which may lead to other treatment advancements.
- It would be unjust to not make this available to those who would benefit from this drug combo.
- Having it exposed to new patients, I believe, will advance cancer treatment's normality, I hope, will give patient and the medical profession a new positivity.

Thank you for your time.

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Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer

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Declared competing interests of the authors

The authors declare that they have no competing interests.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Yen-Fu Chen (Associate Professor) coordinated the project and critiqued clinical effectiveness evidence. Ewen Cummins (Health Economist) critiqued the cost-effectiveness evidence and undertook ERG's modelling. Daniel Gallacher (Research Fellow) critiqued survival analysis in the company submission and advised on ERG's curve-fitting. Alexander Tsertsvadze (Senior Research Fellow) critiqued clinical effectiveness evidence. Osemeke Osokogu (Research Fellow) critiqued the company's decision problem and reviewed data from the literature on patient survival. Anna Brown (Information Specialist) critiqued the company's searches and conducted additional ERG searches. Mubarak Patel (Research Associate) critiqued statistical analysis of the company submission and provided statistical support. Amin Mehrabian (Research Fellow) collated evidence from literature on treatment pathway and patient survival. Ji-Eun park (Research Fellow) collated evidence from literature on the epidemiology and systemic therapies for the condition. Aileen Clarke (Professor) commented on draft versions of the report. Paul Sutcliffe (Associate Professor) helped coordinate the project and provided senior advice. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC).

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIC	Akaike Information Criterion
BEACON ctrl	BEACON CRC trial control arm
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BSC	Best Supportive Care
CI	Confidence Interval
CR	Company's Response (to ERG's clarification questions)
CS	Company Submission
CSR	Clinical Study Report
DOR	Duration Of Response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
ENCO+c	Encorafenib + cetuximab
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union
FAD	Final Appraisal Determination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOLFIRI	Folinic acid + 5-fluorouracil + irinotecan
FOLFIRI+c	Folinic acid + 5-fluorouracil + irinotecan + cetuximab
5-FU	5-fluorouracil
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IRIN	Irinotecan
IRIN+c	Irinotecan + cetuximab

ITT	Intention-To-Treat
IV	Intravenous
IWRS	Interactive Web Response System
KM	Kaplan Meier
LYG	Life Year Gained
MAPK	Mitogen-Activated Protein Kinase
MSI	Microsatellite Instability
NMA	Network Meta-Analysis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Overall Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressive Disease
PFS	Progression-Free Survival
PICC	Peripherally Inserted Central Catheter
PPS	Post-Progression Survival
PR	Partial Response
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	Quality Assessment
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
RoB	Risk of Bias
RR	Response Rate
SAE	Serious Adverse Event/s
SD	Standard Deviation
SLR	Systematic literature review
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
T&T	Trifluridine + tipiracil
TA	Technology Appraisal

TTD	Time to Discontinuation
TTP	Time To Progression
TTR	Time To Response
US	United States
WTP	Willingness To Pay

1 EXECUTIVE SUMMARY

1.1 Critique of the decision problem in the company's submission

- The population and outcomes included in the company submission (CS) are consistent with NICE's final scope.
- Intervention: NICE's final scope included both dual (encorafenib and cetuximab) and triple (encorafenib, binimetinib and cetuximab) therapy. The CS included only dual therapy, justifying the change in the intended marketing authorisation on the basis of findings from the pivotal BEACON CRC trial, which showed a more favourable benefit-risk profile for dual therapy.
- Comparators: NICE's final scope included four comparators: FOLFIRI (Folinic acid, 5-fluorouracil and irinotecan), irinotecan, trifluridine-tipiracil and best supportive care. The CS includes only FOLFIRI and trifluridine-tipiracil.
- The company excluded single-agent irinotecan from CS, citing low usage rate (1.8%) in the NHS and opinions from a survey of oncologists as the rationale. The ERG notes evidence from the literature demonstrating a higher risk of severe diarrhoea for single-agent irinotecan compared with FOLFIRI. ERG's clinical advisors confirm poorer tolerability of single-agent irinotecan and a general preference for using FOLFIRI in clinical practice. Therefore the ERG agrees that FOLFIRI is the most suitable comparator for the proposed place in the treatment pathway. The ERG also agrees with the company that best supportive care is not a suitable comparator in this context.
- Trifluridine-tipiracil was listed as a comparator in NICE's final scope and was included in the CS. ERG notes that while trifluridine-tipiracil is recommended (with no restriction regarding genetic mutation status) for previously treated metastatic colorectal cancer (mCRC) in NICE TA405, it is mainly used in clinical practice as a third- or subsequent-line treatment after two prior therapies failed or cannot be tolerated. While the company suggested that encorafenib dual therapy could replace trifluridine-tipiracil as a third-line therapy in this context, the ERG considers that the technology (if recommended) is most likely to be used as a second-line therapy in clinical practice and is unlikely to be reserved as a third- or subsequent-line therapy, given that currently no other systemic therapy has been recommended in NICE guidelines for treating this specific patient population.

1.2 Summary of the key issues in the clinical effectiveness evidence

- Clinical effectiveness evidence came primarily from a single phase 3, BEACON CRC trial. Treatments received by the comparator group of the trial (cetuximab with either FOLFIRI or

irinotecan) differ from the comparators specified in final scope and the CS (FOLFIRI or irinotecan without cetuximab). As a result, there is no direct comparison evidence to inform cost-effectiveness analysis.

- The ERG discerns that the inclusion of cetuximab in both the intervention and control arms in the BEACON CRC study reflected the clinical uncertainty at the time of trial inception concerning the effectiveness of cetuximab (and epidermal growth factor receptor inhibitors, or anti-EGFRs, in general) in treating patients with BRAF V600E mutant mCRC. The company stated that "the choice of FOLFIRI or irinotecan in combination with cetuximab as the control arm represented the most frequently used therapeutic options among second- or third-line therapies at the time of study initiation in global terms, consistent with European and US guidelines" (CS Document B, Section B.2.3, pages 21-22).
- Subsequent literature, while still not conclusive, generally indicates no significant benefit for using anti-EGFRs in previously treated patients with BRAF mutant mCRC, with some international guidelines recommending against their use in this patient population. Cetuximab is recommended as a first-line treatment for EGFR-expressing, RAS wild-type mCRC in combination with FOLFIRI or FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) but not as a second-line treatment. No existing NICE guidelines include a recommendation for any systemic therapy specifically for patients with BRAF mutant mCRC.
- Despite the above, the use of encorafenib in combination with cetuximab (dual therapy) remains the expected marketing authorisation for this technology in previously treated patients with BRAF V600E mutant mCRC in the UK. The dual therapy was recently approved by the US Food and Drug Administration for the same patient population.
- Evidence from the BEACON CRC trial demonstrated a statistically significant improvement for encorafenib dual therapy compared with a control group of cetuximab in combination with FOLFIRI or irinotecan of 3.4 months in median overall survival (OS), 2.7 months in progression free survival (PFS), as well as an improvement in overall response rates and time to deterioration of health-related quality of life. However, the ERG identified some issues related to risk of bias in the trial, including a lack of blinding and unequal censoring due to unequal study withdrawal between treatment arms, which may impact on the strength of evidence from the trial.
- Given the lack of head-to-head trial evidence that compares encorafenib dual therapy with FOLFIRI (without concomitant cetuximab), the company undertook a simple indirect treatment comparison (ITC) in order to enable this comparison. The ITC was based on two key assumptions of equivalence: (1) between cetuximab and panitumumab, and (2) between FOLFIRI and single agent irinotecan. Both assumptions are difficult to verify as there is

paucity of trial evidence comparing these drugs in the patient group with BRAF V600E mutant mCRC.

- The ERG examined evidence supporting the above two assumptions, and found that there are issues related to indirectness, lack of precision and inconsistency. Therefore the ERG considers estimates from the ITC to be of very low certainty. In view of this, the ERG thinks that the direct comparative evidence from the BEACON CRC trial remains the most reliable data for evaluating clinical and cost-effectiveness of the technology against its comparators despite the presence of cetuximab (which has not been shown to have significant effects) alongside FOLFIRI/irinotecan in the control arm. Clinical evidence from the direct comparison between encorafenib dual therapy and the control arm in the BEACON CRC trial is therefore used in the ERG's base case for cost-effectiveness analysis.
- No direct or indirectly-connected evidence is available for comparing encorafenib with trifluridine-tipiracil in patients with BRAF mutant mCRC. The company carried out a naïve comparison (i.e. between individual arms from different trials with the problem that randomisation was not preserved). In the naïve comparison data from the dual therapy arm of the BEACON CRC trial was compared with data from trifluridine-tipiracil arm of another trial, RECOURSE. As the RECOURSE trial was conducted in patients with mCRC with unknown BRAF mutation status, the company applied further adjustment using hazard ratios for OS and PFS between mCRC with and without BRAF mutation estimated from a further trial to reflect the much poorer prognosis of patients with BRAF mutation. However, the ERG notices that patients in the RECOURSE trial were much more treatment refractory (with the majority having received more than three prior therapies) compared with patients in the BEACON CRC trial (with over half having received only one prior therapy). The ERG therefore concludes that the patient populations in this naïve indirect comparison were too heterogeneous to allow reliable comparison of data between these two trials. We consider that this naïve comparison made by the company is likely to be substantially biased in favour of encorafenib dual therapy.

1.3 Summary of the key issues in the cost effectiveness evidence

Two key issues in the economics relate to the comparison with trifluridine + tipiracil:

- Is trifluridine + tipiracil used at the same point of treatment as sought for encorafenib + cetuximab? While the company suggested that encorafenib dual therapy could replace trifluridine + tipiracil, which is recommended in TA405 as a third-line therapy for mCRC, the ERG considers that encorafenib dual therapy is most likely to be used as a second-line therapy, i.e. in a place earlier in the treatment pathway compared with trifluridine + tipiracil as described in Section 1.1).

- Is the naive comparison with trifluridine + tipiracil valid? This relies upon data from the RECOURSE trial for trifluridine + tipiracil. The ERG thinks that the much higher number of previous treatments in the RECOURSE trial compared to the BEACON trial invalidates this comparison.

For the above reasons the ERG does not present revised cost effectiveness estimates for encorafenib + cetuximab with trifluridine + tipiracil.

For the comparison with FOLFIRI, there is again no direct comparative evidence from RCTs and the company had to resort to an ITC. There is a lot of uncertainty around the results of this ITC, as summarised in the ERG's assessment described above. As the BEACON CRC trial is the only source of reliable evidence on the effectiveness of encorafenib dual therapy, the ERG considers the unadjusted BEACON control arm to be the most suitable proxy comparator that reflects clinical practice in which FOLFIRI is the preferred choice.

Other issues for the comparison with FOLFIRI are:

- Whether the BEACON control arm, composed of FOLFIRI + cetuximab patients and irinotecan + cetuximab patients biases the analysis against FOLFIRI
- Whether applying the BEACON PFS KM curves artificially restricts the tails of the PFS curves, and if so whether this biases the analysis
- Whether time to treatment discontinuation is synonymous with PFS, and whether the BEACON trial suggests a different experience in the encorafenib + cetuximab arm compared to the control arm
- Whether consideration of treatment waning would worsen the cost effectiveness estimate
- Whether the company piecewise analyses presented in the company model need to be presented and considered in more detail.

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG makes the following changes to the company base case:

- ERG01: Applies the ERG piecewise OS parameterised curves estimated using the BEACON trial data, using the exponential for its revised base case
- ERG02: Applies the BEACON trial PFS KM curves
- ERG03: Applies the BEACON FOLFIRI + cetuximab quality of life values for FOLFIRI
- ERG04: Applies the BEACON trial median relative dose intensities
- ERG05: Assumes an initial loading dose for cetuximab, with the subsequent maintenance dose being on day 8, and thereafter fortnightly

- ERG06: Revises the FOLFIRI SAE costs to be based upon BEACON, with an estimated [redacted] average cost per patient
- ERG07: Revises PFS monthly resource use to have no additional administration costs, one outpatient consultation and for FOLFIRI two district nurse visits
- ERG08: Makes some minor corrections to the direct drug costs.

At list prices for all treatments, including encorafenib, this results in the following deterministic estimates for the comparison with FOLFIRI.

Table 1. ICER resulting from ERG's preferred assumptions

	Costs	QALY
FOLFIRI	£13,548	0.571
Encorafenib + cetuximab	£66,329	0.789
Net	£52,781	0.218
ICER	£242,178	

Probabilistic modelling estimates similar central estimates to the deterministic estimates, and that there is no probability of encorafenib + cetuximab being cost effective at willingness to pay values up to £100k per QALY.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertakes the following sensitivity analyses for the comparison with FOLFIRI:

- SA01: Applies the alternative ERG OS functional forms
- SA02: Applies the ERG PFS parameterised curves
- SA03: Applies the Peeters et al HRs to the BEACON control arm ERG OS exponential curve and PFS KM curve
- SA04: Applies the company ITC HRs to the BEACON encorafenib + cetuximab arm ERG OS exponential curve and PFS KM curve
- SA05: Explores the alternative company parameterised curves functional forms, adopting the same form for OS and PFS
- SA06: Equalises PFS quality of life values and PPS quality of life values between the arms at the BEACON trial averages
- SA07: Applies the TA405 CORRECT trial PPS QoL value of 0.59
- SA08: Applies 100% relative dose intensities, and BEACON mean relative dose intensities

- SA09: Assumes no IV drug vial sharing
- SA10: Increases the PPS treatment costs in the encorafenib + cetuximab arm proportionate to the increase in PPS relative to FOLFIRI.

The findings are presented in Table 2 below.

Table 2. Exploratory analyses undertaken by ERG

Analysis	ICER £/QALY
Base case	£242k
SA01a: ERG OS Weibull piecewise from 3 months	£227k
SA01b: ERG OS Gompertz piecewise from 3 months	£139k
SA01c: ERG OS Log-normal piecewise from 3 months	£202k
SA01d: ERG OS Log-logistic piecewise from 3 months	£201k
SA01e: ERG OS generalised gamma piecewise from 3 months	£206k
SA02a: ERG PFS exponential piecewise from 2 months	£245k
SA02b: ERG PFS Gompertz piecewise from 2 months	£258k
SA02c: ERG PFS Log-normal piecewise from 2 months	£280k
SA02d: ERG PFS Log-logistic piecewise from 2 months	£277k
SA02e: ERG PFS generalised gamma piecewise from 2 months	£254k
SA03: HRs applied to BEACON control arm to estimate FOLFIRI	£142k
SA04: HRs applied to BEACON encorafenib arm to estimate FOLFIRI	£149k
SA05a: Company Log-logistic curves for OS and PFS	£242k
SA05b: Company Weibull curves for OS and PFS	£257k
SA06: Quality of life values not arm specific	£212k
SA07: TA405 PPS QoL value of 0.59	£215k
SA08a: 100% relative dose intensities	£251k
SA08b: BEACON mean relative dose intensities	£236k
SA09: No vial sharing	£265k
SA10: Encorafenib + cetuximab PPS cost proportionate to time in PPS	£243k

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This single technology appraisal (STA) concerns the use of encorafenib in combination with cetuximab for treating people with BRAF V600E mutation-positive metastatic colorectal cancer (mCRC).

2.1.1 Incidence of the condition and prognosis

Colorectal cancer accounts for 11% of all new cancer cases in the UK, with 63.7 cases per 100,000 population diagnosed in 2017.[1] Around a quarter of colorectal cancer patients have metastases at diagnosis (stage IV).[2] One-year and five-year survival among these patient is 44% and 10% respectively, compared with 98% and 93% among patients diagnosed at stage I.[3]

BRAF is a gene that encodes a cell-signalling protein (serine/threonine-protein kinase B-raf), which affects pathways related to cell growth, proliferation, differentiation, migration and apoptosis (programmed cell death).[4] Previous studies show that around 10% of colorectal cancer patients are characterised by a mutation in the BRAF gene[5-7] Although the mutation may occur in many locations of the gene, the majority of BRAF mutations occur at amino acid 600 where valine (V) is substituted by glutamic acid (E), hence termed V600E. BRAF V600E mutation characterises up to 80% of all BRAF mutations.[8] Overall survival has found to be far inferior for colorectal cancer patients with a BRAF mutation compared to their BRAF-wild-type (i.e., without mutation) counterparts.[5] For brevity, we refer to BRAF V600E mutation as BRAF mutation in this report. However, it is worth highlighting that longer overall survival has been reported in a small case series for patients with mutations in other locations of the BRAF gene, such as the D594G mutation.[9] Given the rarity of these mutations, it is unclear whether patients with BRAF mutations outside the V600E location represent a subgroup with better prognosis compared with those with V600E mutations.

2.1.2 Molecular biomarker testing in the treatment pathway

The recently updated NICE Guideline on colorectal cancer (NG151) recommends testing for BRAF V600E mutations in all those with mCRC suitable for systemic anti-cancer treatment given its value in predicting treatment response to anti-epidermal growth factor receptor (EGFR) therapy,[10] such as cetuximab and panitumumab. People with BRAF V600E mutant mCRC have been found to be resistant to anti-EGFR therapy.

Tests for BRAF V600E mutations have also been included in NICE Diagnostics Guidance (NG27) published in 2017.[11] This guidance recommends tests for BRAF mutations following an abnormal

finding from molecular testing (offered to all people with colorectal cancer when first diagnosed for identifying Lynch syndrome which is an inherited genetic condition arising from mutations of genes involved in DNA mismatch repair and which is associated with higher risk of colorectal and several other types of cancer). The new NICE guideline [11] expands coverage of BRAF V600E mutation tests to all those with mCRC, including those who previously would not have been offered the Lynch syndrome tests.

In addition to BRAF V600E mutation tests, the new NICE guideline also recommends testing for RAS mutations.[10] RAS genes encode Ras proteins which control pathways that regulate cell proliferation.[12] People with mCRC associated with RAS mutations have also been found to have poor response to anti-EGFR therapy.[13] Notably, RAS and BRAF mutations have been found to be almost mutually exclusive, and therefore people with BRAF mutations are likely to be identified as RAS wild-type. The use of RAS testing in guiding treatment selection was incorporated into clinical practice much earlier than BRAF testing. Consequently, many existing trials of mCRC report RAS mutation status and some of have focused on RAS wild-type populations. These trials may have included some participants with BRAF V600E mutations. The exact proportion is unknown (as the BRAF mutation test was not carried out) but likely small. The applicability of evidence from these trials is limited in the context of this STA.

2.2 Background

2.2.1 Critique of company's overview of current treatment pathway

Overall the ERG found the company's description of the current treatment pathway to be accurate. Systemic anti-cancer therapy was not re-appraised during the update of the latest NICE guideline for colorectal cancer (NG151),[10] and therefore it refers to individual technology appraisal (TA) guidance and the NICE Pathway[14] for the choice of treatments for mCRC. As described in the CS (Document B, Section 1.3.2), while several treatment options are recommended in various TAs and in the NICE Pathway as first-line treatments for mCRC, only trifluridine-tipiracil has been recommended as a subsequent (post first-line) treatment in TA405 guidance[15] and the NICE Pathway. Nevertheless, various treatment options that are recommended in the previous NICE guideline (CG131), while no longer listed in the NICE Pathway, are likely to be clinically relevant:

- FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or
- FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or
- XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment.

Based on this recommended treatment sequence, FOLFIRI and single agent irinotecan are clinically relevant as post-first line therapy and are included in NICE's final scope as comparators for this STA, even though the company rejected single agent irinotecan on the grounds of expert opinion and data from a market survey (see Section 2.3).

Despite the broadened coverage for BRAF V600E mutation tests, the company pointed out (CS Document B, Section B.1.3.2) that current NICE guideline, NICE Pathway and TA guidance do not include specific treatment for the BRAF-mutant population.[10, 14]

2.2.2 Critique of the company's proposed place of the technology in the treatment pathway

The company proposed the use of encorafenib 'following first-line chemotherapy' (CS Document B, Section B.1.3.2.3, page 17). As the key trial underpinning this submission (BEACON CRC)[16] included patients who had received either one or two prior treatment regimens, the evidence would best support decisions concerning the technology's use as the 2nd or 3rd line treatment. As no other treatments have obtained marketing authorisation for this group of patients, the technology would be the first choice for this place in the treatment pathway if it were to receive a positive recommendation.

The ERG is aware of an ongoing, single arm, phase II trial that is investigating the triple therapy of encorafenib, binimetinib plus cetuximab as first line treatment for BRAF V600E mutant mCRC.[17, 18]

2.3 Critique of company's definition of decision problem

Population

The population investigated in the CS (Document B, Section B.1.1, page 8) matches that defined within the NICE final scope, namely people with previously treated BRAF V600E mutation-positive mCRC. It also broadly corresponds with the patient population included in the key trial related to this submission (BEACON CRC).[16]

Intervention

The intervention in the decision problem is encorafenib with cetuximab. This matches the final scope. The company provided a description of the technology along with a draft of the Summary of Product Characteristics. The technology was well described, including its place in the treatment pathway. Previous studies have suggested that combination therapies to sustain inhibition of the mitogen-activated protein kinase (MAPK) signalling pathway, which encorafenib is intended to achieve, might increase survival.[5, 19]

Comparators

Four comparators were listed in the NICE final scope:

• Folinic acid plus fluorouracil plus irinotecan (FOLFIRI)

• Irinotecan

• Trifluridine-tipiracil (only after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable)

• Best supportive care.

The company selected two of these comparators: FOLFIRI and trifluridine-tipiracil. The company did not consider best supportive care as an appropriate comparator since it is reserved for instances where other treatment regimens have failed and therefore its use is reserved for later in the treatment pathway. The ERG agrees with this. The company did not include single-agent irinotecan because of its low prevalence of use after first-line treatment (CS Document B, Section B.1.1, Table 1, page 8). They cited data from the NHS and 11 practising oncologists. The ERG learns from its clinical advisors that FOLFIRI is generally the preferred option over single-agent irinotecan, which requires higher doses when given alone and is poorly tolerated due to toxicity. The ERG's examination of the literature (see Section 3.5.2.1) also confirms that irinotecan is associated with significantly higher risk of severe (grade 3 or 4) diarrhoea compared with FOLFIRI. Therefore the ERG agrees that FOLFIRI is the most suitable comparator for this STA.

The ERG notes that while trifluridine-tipiracil is recommended (with no restriction regarding genetic mutation status) for previously treated metastatic colorectal cancer (mCRC) in NICE TA405,[15] it is mainly used in clinical practice as a third- or subsequent-line treatment after two prior therapies have failed or could not be tolerated. While the company suggested that encorafenib dual therapy could replace trifluridine-tipiracil in this context, the ERG considers that the technology is most likely to be used as a second-line therapy and therefore occupies an earlier place in the treatment pathway compared with trifluridine-tipiracil.

Outcomes

All the outcome measures considered in NICE final scope were investigated by the company. They are overall survival (OS), progression-free survival (PFS), response rates (RR), adverse effects and health-related quality of life (HRQoL).

Table 3. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with previously treated BRAF V600E mutation-positive mCRC.	As per scope	N/A	The population defined in the final scope could cover people who have received any number (one or more) of prior therapies. In the key trial, people who previously received either one or two regimen(s) were included. Therefore evidence included in this submission is most applicable to patients with a similar treatment history.
Intervention	• Encorafenib with cetuximab • Encorafenib with binimetinib and cetuximab	Encorafenib with cetuximab	In line with the decision by Pierre Fabre to only pursue marketing authorisation for the dual therapy of encorafenib with cetuximab. The triple combination of encorafenib + binimetinib	The intervention described in the company submission partially matches the intervention described in the final scope. Triple therapy was removed as explained by the company.

			with cetuximab is no longer relevant to decision making in England and has been omitted from the company decision problem.	Decision on marketing authorisation for the dual therapy – encorafenib plus cetuximab – is awaited.
Comparator(s)	• Folinic acid plus fluorouracil plus irinotecan (FOLFIRI). • Irinotecan. • Trifluridine-tipiracil (only after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable). • BSC.	• Folinic acid plus fluorouracil plus irinotecan (FOLFIRI). • Trifluridine-tipiracil (only after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable).	BSC • BSC refers to supportive care to manage the symptoms and complications of the condition, when patients have exhausted all active treatment options (due to failure, lack of tolerability or contraindicated). The anticipated use of encorafenib with cetuximab would be earlier in the treatment pathway, where active treatments are still available (i.e., FOLFIRI or trifluridine-tipiracil).	Of the four possible comparators in the final NICE scope, the company selected two comparators: FOLFIRI and trifluridine-tipiracil. ERG finds evidence (see Section 3.5.2.1) that irinotecan single therapy is associated with higher risk of severe diarrhoea and is less well tolerated compared with FOLFIRI, which is confirmed by our clinical advisors. ERG therefore agrees that FOLFIRI is a more suitable comparator.

			• Therefore, BSC is not considered to be an appropriate comparator and will not be considered in the company decision problem. Irinotecan • The use of single-agent irinotecan as per the marketing authorisation is not considered a relevant comparator after first-line treatment. Data based on patient-level information collected by the NHS† shows use of single-agent irinotecan accounted for only 1.8% of therapies used at second-line by patients with mCRC (CS Document B, Section B.1.3.3.2, page 17). Responses from 11	The ERG notes that trifluridine-tipiracil is mainly deployed in clinical practice as a third- or subsequent-line therapy. Therefore, while the company suggested that encorafenib dual therapy may replace trifluridine-tipiracil as a third-line therapy, the ERG discerns that the technology is most likely to be used as a second-line therapy given the lack of other recommended systemic therapy for this specific patient population, and therefore be used before trifluridine-tipiracil in the treatment pathway. Consequently, trifluridine-tipiracil may not be the most relevant comparator.

			practicing oncologists who were consulted on treatment usage for BRAF-mutant mCRC also showed that single-agent irinotecan is rarely used as a second-line agent (n=1/11) and additional expert input[1] sought for this submission further supports this. (CS Document B, Table 1, page 9) • Therefore, single-agent irinotecan is not considered to be an appropriate comparator and will not be considered in the company decision problem.	

[1] Two research activities were conducted to elicit information and test assumptions for the submission. Overall these two exercises elicited responses from three NHS consultant oncologists practicing in England: 1. Advisory board attended by two NHS consultant oncologists practicing in England, and three health economists; 2. Face to face meeting followed by telephone follow-up with an NHS consultant oncologist practicing in England.

Outcomes	• The outcome measures to be considered include: – OS. – PFS. – Response rates. – Adverse effects of treatment. – HRQoL.	As per scope	N/A.	The outcomes in the company's submission match the outcomes described in the final NICE scope. The company focused on appropriate outcomes.
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.	Not described in the Decision problem table (CS Document B, Table 1, pages 9-10)	N/A	While not explicitly described in the Decision problem table, the company's approaches to economic analysis is broadly in line with the final scope. The 10 year time horizon adopted in the company's reference case is considered sufficiently long as 5-year survival for people with mCRC is only 10% overall, and the prognosis for BRAF mutant mCRC patients is

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of encorafenib in dual or triple therapy is conditional on the presence of BRAF V600E mutation. The economic modelling should include the costs associated with diagnostic testing for BRAF V600E mutation 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.			substantially poorer than average. Although the use of encorafenib dual therapy is conditional on the result of BRAF mutation testing, the test 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.
Subgroups	None listed	Not described in the Decision problem table.	N/A	No subgroup was mentioned in the final scope. Limited subgroup analyses were

				presented in the CS and explored by the ERG.
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.	Not described in the Decision problem table.	N/A	The technology is still awaiting marketing authorisation when the ERG report is prepared. The BEACON CRC trial [16] provides the key evidence for both the application of marketing authorisation and CS for this appraisal.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company undertook two systematic literature reviews (SLRs): one for randomized controlled trials (RCTs) and, when limited RCT evidence was found for patients with BRAF V600 mutation, a further SLR for non-RCT evidence in that specific population (see CS Document B Appendices, section D.1). Overall, the literature search strategies for both SLRs were reasonably comprehensive and it is unlikely that any additional clinical studies that focused on the BRAF mutant mCRC population were missed, although there is a possibility that some studies which reported results from BRAF mutant population as a subgroup were not captured. Detailed critique of the search strategies for the company SLRs can be found in Appendix 1 on page 123.

3.1.1 SLR of RCTs

The specified inclusion criteria were much broader than the decision problem in terms of population and treatments (intervention and comparators) and covered adult patients with RAS wild-type or BRAF V600E mutant metastatic or irresectable mCRC. Patients receiving 1st, 2nd and 3rd line treatment were all included. In total 128 publications reporting findings from 84 trials were identified to meet the inclusion criteria. Nevertheless, the submission then focused only on 11 RCTs in which findings from patients with BRAF mutations receiving 2nd or subsequent lines of treatment were presented. Of these studies, three were RCTs carried out exclusively in patients with BRAF V600E mutations (including the BEACON CRC trial) and eight were RCTs covering wider patient populations but separately reported findings from the subgroup of patients with BRAF mutations. Key findings related to OS and PFS from these trials are shown in CS Document B Appendices Table 3 (pages 29-30). Quality assessment of eight of these studies are presented in CS Document Table 7 (page 45; BEACON CRC) and in CS Document B Appendices Table 6 (pages 69-70; comparator trials). Quality assessment was not carried out for the three remaining trials as these were only available as abstracts. The 11 RCTs included diverse intervention and comparator treatments and were put forward to be considered in the company's indirect treatment comparison (ITC) and network meta-analysis (NMA) – see Section 3.3.

In addition to the 11 RCTs that best match the decision problem in terms patient population and lines of treatment, the company also identified 52 RCTs reported in 75 publications/abstracts pertaining to first line treatment for patients with mCRC (although not specifically with BRAF mutations). These were not further examined in the CS.

3.1.2 SLR of observational studies

Inclusion criteria for this SLR were similarly broad, with the only difference being study design. Overall, 24 non-RCTs meeting the inclusion criteria were identified. Of these, four prospective and six retrospective non-RCTs which reported outcomes for interventions in patients with BRAF V600E mutations were retained and put forward to be considered for ITC/NMA. Quality assessment was not performed and findings were not presented for these studies. The remaining 14 observational studies which met the initial inclusion criteria but did not focus on interventions were not examined further.

Overall, the ERG is satisfied with the company's study selection process and quality assessment, although the ERG found the study selection criteria not very well specified and noted that there were conflicting statements with regard to the data extraction process (CS Document B Appendices, pages 25 and 82).

The ERG agrees that the 11 RCTs prioritised in the SLR of RCTs are most relevant for this STA and examines their characteristics and findings in further detail (see Section 3.5). Given the very limited evidence for 2nd and subsequent lines of treatment in the BRAF V600E mutant mCRC population, the ERG also explored potentially useful data in the 52 RCTs pertaining to first line treatment in the broader mCRC population captured by the company SLR, as well as the 14 observational studies reporting survival outcomes not considered by the company. The findings are reported in Section 3.5.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

Although the company's SLR identified 11 potentially relevant RCTs investigating the intervention and/or comparators, the CS focused on a single study (BEACON CRC trial)[16] that used the technology of interest (encorafenib with cetuximab) in people with BRAF V600E-mutant mCRC (CS Document B; pages 20-57). Among the 11 RCTs found in the company SLR, the ERG notices another trial (published only as a conference abstract) in which encorafenib and cetuximab as double therapy was compared with a triple therapy with the addition of alpelisib, an inhibitor of the PIK3CA gene which has also been found to be mutated in some patients with CRC.[20] As alpelisib is not licenced for treating mCRC and is not a comparator of interest, and the dose of encorafenib investigated (200 mg once a day) is lower than the recommended dose (300 mg once a day), the trial is only briefly examined in Section 3.5. No meta-analysis was presented in the CS and the ERG does not think any other important RCTs of the technology have been omitted.

The BEACON CRC trial is a global, multicentre open-label phase-III randomised active controlled trial (RCT) in a population with BRAF V600E-mutant metastatic colorectal cancer (mCRC) patients.

The trial constitutes the main body of evidence included in the CS. The objective of the BEACON CRC trial dat used in the context of this CS was to determine if the use of combination of encorafenib with cetuximab (dual therapy) leads to improved survival compared to control treatment in patients with BRAF V600E–mutant mCRC.

The BEACON CRC trial was a three arm trial in which the dual therapy of interest (encorafenib and cetuximab, n=220) was compared with a triple therapy (encorafenib and cetuximab plus binimetinib, N=224) and a control group (cetuximab combined with either FOLFIRI or single agent irinotecan, N=221). However, as a more favourable benefit-risk profile was observed in the trial for the dual therapy, the company sought marketing authorisation only for the dual therapy and therefore this STA only concerns dual therapy. The primary endpoints for the trial concerned comparison between the triple therapy and the control; the comparisons of encorafenib with cetuximab vs. control were assessed as secondary endpoints, and these analyses were presented as key evidence in the CS. The efficacy and safety data set with a cut-off on 15 August 2019 was presented as the key evidence, representing the final and most mature analysis available. Given that data from the triple therapy arm of the BEACON CRC trial are not relevant to this assessment, the ERG will also only focus on the dual therapy and control arms of the trial in the rest of this report.

3.2.1 Summary of study methodology

The summary of the BEACON CRC trial and patient characteristics is provided in Table 3 (CS Document B, page 20). Briefly, the BEACON CRC trial compared encorafenib with cetuximab (Encorafenib with cetuximab; n=220 randomised) to the investigator's choice of chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab (control arm; n=221 randomised). The BEACON CRC trial included patients with BRAF V600E-mutant mCRC whose disease had progressed after one or two prior regimens in the metastatic setting.

CS Document B provides information on trial design/methodology (pages 21-32; Figure 1) and statistical analysis (pages 35-44; Figure 2; Tables 5-6). For convenience, the summary methodology of this trial has been reproduced in Table 4 below:

Table 4. Summary of methodology (BEACON CRC trial)

Trial name	BEACON CRC
Location	221 sites in 28 countries: 111 sites in Europe, 36 sites in North America and 74 sites in selected countries from the rest of the world. [redacted] UK sites (n=[redacted] patients)
Trial design	Multicentre open-label phase-III randomised active controlled trial
Planned interim analysis	Prospectively defined to be performed when ≥169 OS events are accrued in the encorafenib with cetuximab and control arms combined
Duration of the study	As of 15th August 2019, the median duration of follow-up for survival was 12.8 months
Method of randomisation	IWRS and a computerised central randomisation list, randomised 665 patients at a 1:1:1 ratio to the three study treatment arms
Method of blinding	An open-label study where investigators, patients, and a limited number of study personnel knew the study treatment assigned. The sponsor, trial design team and the independent review committee were blinded to treatment assignment to minimize information/allocation bias
Study participants	Patients diagnosed with BRAF V600E-mutant mCRC
Intervention	28-day treatment cycles continued until disease progression, unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death or lost to follow-up: • Encorafenib [300 mg QD] with cetuximab [400 mg/m^2 initial and then 250 mg/m^2 IV QW] (n=220 patients randomized) • Encorafenib [300 mg QD] + binimetinib [45 mg BID] with cetuximab [400 mg/m^2 initial and then 250 mg/m^2 IV QW] (n=224 patients randomized)
Comparator	Investigator's choice of either (n=221 patients randomized): • Irinotecan [180 mg/m^2 IV Q2W]/cetuximab [400 mg/m^2 initial and then 250 mg/m^2 IV QW] (n –not reported) • FOLFIRI [IV Q2W]/cetuximab [400 mg/m^2 initial and then 250 mg/m^2 IV QW] (n – not reported)
Primary outcome	OS and ORR for encorafenib + binimetinib with cetuximab (not included in the CS for marketing authorization)

Key secondary endpoint	OS (defined as the time from randomisation to death due to any cause)
Other secondary endpoints	PFS (defined as the time from randomisation to the earliest documented date of disease progression, per RECIST (version 1.1) [21] and as determined by investigator, or death due to any cause
	ORR (confirmed by investigator or BICR, defined as the number of patients achieving a BOR or CR or PR divided by the total number of patients in that treatment arm
	DOR (confirmed by BICR and investigator, defined as the time from first radiographic evidence of response to the earliest documented progressed disease or death (calculated for responders only)
	TTR (confirmed by BICR and investigator, defined as the time from date of randomisation to date of first radiographic evidence of response (CR or PR)
	Patient reported outcomes (HRQoL measures): EORTC QLQ-C30, FACT-C, EQ-5D-5L, and PGIC
	Adverse events
Statistical methods	Three major population datasets were defined for data analyses: FAS, PPS, and SS. Endpoints for OS and PFS were derived using the KM method, and the HR and 95% CIs were estimated using Cox proportional hazard models, adjusted for randomization stratification factors. Formal statistical testing was done with a hierarchical approach using Lan-DeMets spending function that approximated the O'Brien-Fleming boundaries to account for multiple testing during interim and final analyses. The significance α level for the dual therapy vs. control was 0.0042 for OS and 0.0117 for PFS
Sample size calculation	A total of 338 deaths were needed to detect HR=0.70 with 90% power at a one-sided significance level of 0.025 for OS for the encorafenib + cetuximab vs. control comparison. The ERG was able to replicate this calculation using the power logrank command in StataSE 15 (64-bit)
Concomitant therapies	Concomitant therapies were permitted except for other anticancer agents (e.g., cytotoxic chemotherapy, small molecule targeted agents, biological agents, immune response modifiers or hormonal

	therapy), radiation therapy (not including palliative radiotherapy at focal sites that covered ≤10% of the bone marrow reserve), herbal preparations/medications, strong systemic CYP3A4 inhibitors, combination anticholinergic medications (containing barbiturates or other agents in patients receiving irinotecan)
Subgroup analysis (pre-planned)	Subgroups were pre-specified for OS, ORR and PFS with at least 10 patients based on ECOG PS, prior use of irinotecan, cetuximab source, region, number of prior regimens, race, age, gender, number of organs involved at baseline, MSI, BRAF V600E mutation per central assessment, CEA, CRP, removal status of primary tumour, side of tumour, presence of liver metastases at baseline. The OS and PFS analyses were to include KM summaries and HRs (95% CI) from unadjusted Cox models and forest plots were also provided
Sensitivity analysis (pre-planned)	OS (per-protocol set, unadjusted Cox regression/FAS, adjusted multivariate Cox regression) ORR (unadjusted Chi-squared test, FAS, patients who had measurable disease at baseline in Phase 3/RES, multivariate adjusted Cox regression)
HR=hazard ratio; OS=overall survival; RECIST=Response Evaluation Criteria in Solid Tumors; PFS=progression-free survival; ORR=overall response rate; BICR= blinded independent central review; BOR=best overall response; CR=complete response; PR=partial response; DOR=duration of response; TTR= time to response; AE=adverse events; HRQoL=health-related quality of life; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-C=Functional Assessment of Cancer Therapy-Colon Cancer; EQ-5D-5L=EuroQoL-5 dimensions-5 levels; PGIC=Patient global impression of change; KM=Kaplan-Meier; 95% CI=95 percent confidence interval; FAS=full analysis set; IWRS= interactive web response system; ECOG PS=Eastern Cooperative Oncology Group Performance Status; CRP=c-reactive protein; CEA=carcinoembryonic antigen; RES=response efficacy set; FAS=full analysis set; PPS=per-protocol set; SS=safety set	

3.2.2 Patient disposition and withdrawals

The 665 patients randomised were allocated to receive either the triple therapy of encorafenib plus binimetinib with cetuximab (n=224), the dual therapy with encorafenib plus cetuximab (n=220), or the control active treatment of investigator's choice (n=221) with either irinotecan/cetuximab or FOLFIRI/cetuximab.

The ERG noted that of patients allocated to the three treatment arms, 34 did not receive the treatment, of whom 28 (82%) were from the control arm. Specifically, more patients did not receive treatment in the control arm (28/221,13%) vs. the encorafenib with cetuximab arm (4/220, 2%), most of them being due to withdrawal of consent. According to the company response (CR; Question A6, page 127): "*Randomised but not treated patients were followed-up for efficacy and safety measures until their study withdrawal, in the same way as other patients*." The patients who were randomised, but not treated, were included in the FAS and the Response Efficacy Set (RES), but not in the Safety Set (SS) or the Per Protocol Set (PPS). For efficacy measures, randomised but not treated patients were censored using the same rules as for other patients (CR Question A6, page 127).
Among patients receiving study treatment (data cut-off 15th August 2019), the rate of treatment discontinuation was higher in the control arm (186/193, 96%) vs. the dual therapy arm (186/216, 86%) (CS Document B Appendix D; Table 14, page 112). Specific reasons for discontinuation which occurred at different rates between the two arms were progressive disease, change in patient condition, adverse events/tolerability of treatment, death, withdrawal of consent and dose interruption.

According to the CR to ERG clarification questions (CR Question A1, Table 1, page 3), the control arm (n=221; full analysis set) included two groups, one receiving FOLFIRI with cetuximab (n=129) and the other irinotecan with cetuximab (n=92). Only few patients in the control arm switched the therapy from receiving FOLFIRI with cetuximab to irinotecan with cetuximab (n=[redacted]) or from receiving irinotecan with cetuximab to FOLFIRI with cetuximab (n=[redacted]) (CR Question A7, Tables 36-37).

The ERG noted that the median duration of treatment in the control arm was much shorter compared to encorafenib with cetuximab arm (7 weeks vs. 19.3 weeks). About 61.1% of patients received ≥16 weeks of study treatment in the encorafenib with cetuximab arm; by comparison only one-fifth of patients in the control arm (22.3%) received ≥16 weeks of study treatment (CS Document B; page 69) (ARRAY-818-302 CSR Addendum; Table 3, page 14).[22]

3.2.3 Baseline patient characteristics

The majority of baseline demographic and clinical characteristics of the participants randomised in the trial were comparable across the treatment groups (CS Document B; Table 4, page 34). However, the ERG noted some imbalances in sex (female 47.7% vs. 57.5%), ethnicity ([redacted]), and tumour location ([redacted] for encorafenib dual therapy vs. control group. The potential impact of these on treatment outcomes is unclear.

In order to explore the potential influence of the choice of therapy in the control group (FOLFIRI+ cetuximab vs irinotecan + cetuximab), the ERG requested additional data. The CR provided the distribution of baseline patient characteristics separately for the two therapy groups of the control arm (CR Question A1, Table 1, page 3). There was no major imbalance in the baseline patient characteristics between the two therapy groups except for the [redacted] in the FOLFIRI+ cetuximab group compared with irinotecan + cetuximab group. [redacted] was observed among patients with only 1 prior mCRC therapy, but not in patients with ≥2 prior mCRC therapy (CR Question A8, Tables 38-39, page 130).

3.2.4 Efficacy outcomes

In the BEACON CRC trial, encorafenib dual therapy compared to the control treatment showed significant improvements in OS (39% risk reduction), PFS (56% risk reduction), ORR (19.5% vs. 1.8%), and delayed deterioration (median time to definitive 10% deterioration) in HRQoL measures (EORTC QLQ-C30, FACT-C, and EQ-5D-5L) (CS Document B; Tables 9-10 and Figures 3-4; ERG report). The company provided arm-specific numbers to support their statement that HRQoL measures were improved in the encorafenib with cetuximab arm compared to the control arm (CS Document B; pages 54-55). Hazard ratios and 95% CIs for HRQoL measures for the between-arm difference were provided at a subscale level in the CR and indicated significant improvements in favour of encorafenib with cetuximab (CR; Question A11, Table 44, page 134). At follow-up, there was no significant difference between encorafenib plus cetuximab and the control arm in duration of response (DOR) and time to response (TTR).

The ERG noted that based on the visual inspection of KM plot for PFS (CS Document B; Figure 4), the proportionality assumption for PFS (HR=0.44, 95% CI: 0.35, 0.55) may have been violated given the gradual convergence of probability curves of the encorafenib with cetuximab and control arms at about 14 months of treatment. This invites questions regarding the maintenance of superiority of encorafenib with cetuximab in improving PFS compared with control beyond 12 months of treatment.

Table 5. Efficacy outcomes after follow-up (the BEACON CRC trial)

Outcome	Encorafenib with cetuximab [n=220]	Control [n=221]	Difference between the study groups (Point Estimate [PE] and 95% CI, p value)
Primary outcome			
N/A	N/A	N/A	N/A
Key secondary outcomes			
OS	Median # months: 9.30 95% CI: 8.05, 11.30	Median # months: 5.88 95% CI: 5.09, 7.10	HR=0.61 (0.48, 0.77), p<0.0001
Other secondary outcomes			
PFS	Median # months: 4.27 95% CI: 4.07, 5.45	Median # months: 1.54 95% CI: 1.48, 1.91	HR=0.44 (0.35, 0.55), p<0.0001
ORR	43 (19.5%) 95% CI: 14.5, 25.4	4 (1.8%) 95% CI: 0.5, 4.6	PE: NR p<0.0001
DOR	[redacted]	[redacted]	[redacted]
TTR	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30	[redacted]	[redacted]	[redacted]
FACT-C	[redacted]	[redacted]	[redacted]

EQ-5D-5L (VAS and utility score score)	[redacted]	[redacted]	[redacted]
PGIC (cycle 2, 3 and 4)	[redacted]	[redacted]	[redacted]
#=number; PE=point estimate; VAS=visual analog scale; N/A=not applicable; HR=hazard ratio; 95% CI=95 percent confidence interval; OS=overall survival; PFS= progression-free survival; ORR=overall response rate; DOR=duration of response; TTR= time to response; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-C= Functional Assessment of Cancer Therapy-Colon Cancer; EQ-5D-5L= EuroQoL-5 dimensions-5 levels; PGIC=Patient global impression of change; NR=not reported			

The sensitivity analyses results conducted for OS and ORR (CS Document B; section B.2.5.5, pages 42-43 and section B.2.7.1.1.2., pages 50-52) were consistent with the primary analyses for OS and ORR respectively.

The company stated that subgroup analysis results were generally consistent with overall results, showing HRs (OS, PFS) and Odds Ratios (ORs) in favour of encorafenib with cetuximab versus control (CS Document B; page 57 and Appendix A; Figure 4, pages 115-116). The ERG agrees with the company's assessment of subgroup effects.

3.2.5 Safety outcomes

Adverse events (AEs) were analysed based on the safety set (SS; patients who received at least one dose of study drug and had at least one post-treatment assessment), including 216 patients in the encorafenib with cetuximab arm and 193 patients in the control arm (Appendix D; Figure 3, page 111). The company presented the data on AEs in Document B (Tables 15-17; pages 69-75). For convenience, the ERG report provides a table for selected AEs (Table 3). The CR provided the proportions of AEs between the two therapy groups of the control arm (safety set): FOLFIRI with cetuximab vs. irinotecan with cetuximab (CR, Question A13, Tables 46-48, pages 136-142). In general, the frequency of all-grade AEs and SAEs was comparable between the two groups except for

a higher proportion of patients with [redacted] in the FOLFIRI with cetuximab vs. irinotecan with cetuximab group.

In general, the occurrence of all AEs was comparable across the study arms. Regarding specific AEs (reported in >30% patients), the control arm experienced higher rates of diarrhoea ([redacted] and dermatitis acneiform [redacted] compared to the encorafenib with cetuximab arm. However, amongst less frequent AEs [redacted] There was no notable imbalance between the study arms in the incidence of specific SAEs, with the exception of diarrhoea (Grade 3+), which occurred in [redacted] in the control arm but [redacted] in the encorafenib dual therapy arm.

The company stated that in general encorafenib with cetuximab and the control treatments showed comparable toxicity and tolerability profiles. Given the data, the ERG agrees that encorafenib with cetuximab and the control treatments exhibited comparable safety profiles. In considering the safety profiles of the two arms, it should be noted that exposure to the drug for the control arm was much more limited (i.e., shorter) than that for encorafenib with cetuximab.

Table 6. Safety outcomes (adverse events) at follow-up (the BEACON CRC trial): cut-off 15 August 2019

Safety data	Encorafenib with cetuximab n (%) [n=216]	Control n (%) [n=193]
All events (at least one; all grades)		
On-treatment deaths[£]	[redacted]	[redacted]
All AEs	[redacted]	[redacted]
Treatment-related AEs	[redacted]	[redacted]
All SAEs	[redacted]	[redacted]
Treatment-related SAEs	[redacted]	[redacted]
AEs leading to discontinuation of all study treatment	[redacted]	[redacted]
Specific AEs reported in >30% patients (at least one; all grades)		
Diarrhoea	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]
Specific SAEs reported in >2% patients (at least one; all grades)		
Intestinal obstruction	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Cancer pain	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Ileus	[redacted]	[redacted]
Large intestinal obstruction	[redacted]	[redacted]
SAE=serious adverse event; AE=adverse event		

[£] Deaths occurring during treatment or within 30 days of the last dose due to AEs or disease progression. Most on-treatment deaths were attributed to disease progression

3.2.6 Statistical methods

The ERG deems the method for addressing multiple testing and controlling type-I error described in the CS as appropriate. Also, the ERG was able to replicate the company's power calculation results using the 'power logrank' command in Stata15.

Given the visual inspection of KM and log-cumulative hazard plots for OS (CS Document B, Figure 3, page 49; and Figure 8, page 105 respectively), the ERG does not consider that the proportional hazards assumption was violated. There were no scaled Schoenfeld residuals vs. time plots provided to test for the independence between residuals and time, both globally and for separate covariates. However, as the assumption of proportional hazards was not violated given the visual inspection of KM plots and the log-cumulative hazard plot presented in the company's cost-effectiveness section (CS; Figure 8), the ERG agree that the use of the multivariate Cox regression model was appropriate. The KM plot of PFS for the encorafenib dual therapy vs. control comparison found in CS Document B (Figure 4, page 53), shows the probability of PFS for each of the treatment group starting to converge after eight months and meeting around 14 months, thereby violating the assumption of constancy of proportional hazards. The cumulative hazard plot provided by the company in their cost-effectiveness section (CS Document B, Figure 9, page 105) also supported that the assumption of proportional hazard was not appropriate, suggesting that the hazard ratios may be unreliable.

As the company stated (CS Document B; page 43), missing data were imputed according to the rules pre-specified in the statistical analysis plan (SAP) for BEACON CRC. These rules were not described in either Document A or B, so the ERG is unable to judge the validity of any methods used. Censoring rules were described in Document B (section B.2.5.6 and Table 6; pages 43-44). The ERG considers the company's approach on censoring OS and PFS as adequate.

The ERG considers the sensitivity and subgroup analyses of the company to be appropriate. The hypotheses on subgroups were pre-specified and were based on pre-randomised baseline subgroup values. Although the ERG agrees with the company's results of subgroup analysis, given the small samples, the findings for several subgroups were difficult to interpret, especially when the BEACON CRC trial was not designed and powered to test for differences within patient subgroups. However, the ERG notes that the subgroup analyses were not data-driven since they were specified at baseline and pre-randomization. This approach is known to minimize the probability of false-positive findings.[23] The ERG did not find any evidence that the company addressed multiple testing or adjusted the statistical significance levels for these subgroup analyses. Also, it would be desirable if the company presented a biological plausibility rationale supporting their choice of the subgroups analysed.

3.2.7 Risk of bias assessment of the BEACON CRC trial

The risk of bias assessments of the BEACON CRC trial by both the company and the ERG are presented in Appendix 2 of the ERG report (Table 57). The company judged all domains of risk of bias as 'low', but the ERG considers the risk of bias to be unclear or high across several domains

including similarity of randomised groups at baseline, blinding of patients, caregivers, and investigators, between-arm imbalance in dropouts/withdrawals, and intention-to-treat (ITT) analysis/missing values. For example, the ERG notices that substantially more patients in the control arm withdrew before receiving treatment (n=28) compared with the intervention arm (n=2) with the main reason being withdrawal of consent, and that a [redacted] of untreated patients in the control arm [redacted] compared with the overall trial population [redacted] (CSR, p.167). Moreover, lack of blinding, i.e., knowledge of the treatment assigned might have influenced subjective outcomes such as PROs (health-related quality of life measures). The RoB domain for ITT analysis/missing values was judged as 'unclear RoB' because the ERG was unable to assess [due to lack of information] how the company addressed missing values to perform ITT analysis.

3.2.8 Summary statements on the methodology and evidence worth of consideration

- In the BEACON CRC trial, the encorafenib plus cetuximab dual therapy compared to the control treatment (FOLFIRI or irinotecan with cetuximab) showed significant improvements in OS, PFS, ORR, and delayed deterioration (median time to definitive 10% deterioration) in HRQoL measures (EORTC QLQ-C30, FACT-C, and EQ-5D-5L)
- There was no difference at follow-up in duration of response and time to response between the study arms
- The ERG considers that in general, safety profiles of encorafenib with cetuximab and the control treatment are comparable
- The median duration of treatment was shorter in the control arm compared to the intervention arm (encorafenib with cetuximab)
- Although the majority of baseline participant characteristics were comparable across treatment groups, there was some imbalance in the distribution of sex, ethnicity, and primary tumour location between the treatment arms
- The ERG considers the statistical methods used by the company to be appropriate and adequate. However, the company did not describe how missing values were handled
- The KM plot of PFS for the encorafenib dual therapy vs. control comparison showed PFS curves starting to approach each other after eight months and converge around 14 months, thereby violating the assumption of constant proportional hazards
- The BEACON CRC trial had a small patient sample in the UK ([redacted] sites; [redacted] patients)
- The ERG noted 'high/unclear RoB' for several domains of bias in the BEACON CRC trial
- The ERG considers the sensitivity and subgroup analyses to be adequate, except between the subgroups of patients receiving different treatments (FOLFIRI or irinotecan) in the control arm, for which no subgroup analysis was reported by the company and for which the ERG

carried out exploratory analyses using data supplied in CR to ERG clarification questions (see section 3.5.2.1). The BEACON CRC trial was not designed and powered to test these differences between the patient subgroups.

3.3 Critique of trials identified and included in the indirect treatment comparison (ITC) and naïve comparison

As described in Section 3.1.1, the company SLR of RCTs identified and included 11 trials of second- or later-lines of therapy,[16, 24-33] of which three (including BEACON CRC)[16, 24, 25] reported the results of studies exclusively involving patients with BRAF mutations. Eight studies were conducted in mixed populations but reported efficacy results for a subgroup of patients with BRAF mutations (Appendix D; Table 2, Pages 28-29). Of these, two studies[24, 25] were excluded from the synthesis for having a comparator not relevant to the NICE decision problem. Thus, the BEACON CRC (with exclusively mCRC patients with BRAF mutations) and eight other RCTs in mixed populations were included in the evidence mapping (CS Document B, page 61). The mapped evidence network of RCTs revealed a lack of common comparators leading to disconnected networks between the BEACON CRC and other trials (CS Document B; Figure 5, page 62). As a results, a further seven studies[27-33] were excluded from the synthesis because either their comparators were not relevant to the NICE decision problem or they did not have a common comparator (Appendix D; Table 11, page 105).

Consequently, only one RCT (Peeters et al. 2010/2015)[26, 34] apart from the BEACON CRC trial was retained by the company for a potential ITC. Given certain assumptions (see Section 3.4), the Peeters et al. 2010/2015 study could be connected to the BEACON CRC trial,[16] which would allow an ITC of encorafenib with cetuximab vs. FOLFIRI. The company SLR did not identify any studies of trifluridine-tipiracil in mCRC patients with BRAF V600E mutations. In order to allow some comparison of the technology against trifluridine-tipiracil, the company chose the intervention arm of the placebo-controlled RECOURSE trial[35] in patients with mCRC in whom BRAF mutation status was not determined, as the basis for a naïve comparison. The ERG's critique of these two trials is described below.

3.3.1 Critique of Peeters 2010/2015 included in company's ITC vs. FOLFIRI

The Peeters et al. 2010/2015 study was a phase-III open-label RCT (n=421) that compared FOLFIRI with panitumumab to FOLFIRI alone in a mixed mCRC population, which included a subgroup of 45 BRAF-mutant patients. This trial was selected under the assumption that panitumumab has similar effects when compared with cetuximab, as no trial of cetuximab plus FOLFIRI versus FOLFIRI was found. Such a trial would allow the connection of an evidence network between encorafenib plus cetuximab and FOLFIRI, through cetuximab plus FOLFIRI as a common comparator in the mCRC

BRAF mutant population. The ERG independently assessed the RoB of the Peeters et al. 2010/2015 study and rated most domains as at high RoB (see ERG report Appendix 2). The ERG and the company's assessments (Appendix D; Table 6, page 69) on the RoB agreed. The trial authors did not report baseline characteristics for the BRAF mutation subgroup of patients. Also, it was not clear how these characteristics were distributed between the treatment arms compared within this subgroup. Randomisation, treatment allocation concealment, and follow-up methods were not reported. The baseline characteristics (entire sample; n=421) and efficacy (BRAF-mutant subgroup; n=45) results from Peeters et al. 2010/2015 study are presented in Appendix D (Tables 12 and 13, pages 107-108). The study results for the BRAF-mutant subgroup of patients indicated improved OS (HR=0.64, 95% CI: 0.32, 1.28)[26] and PFS (HR=0.69, 95% CI: 0.32, 1.49)[26] in favour of the combination therapy (FOLFIRI with panitumumab) compared with FOLFIRI alone (Appendix D; Table 13, page 108). However, the results are not statistically significant and the estimated HRs have very wide confidence intervals.

3.3.2 Critique of the RECOURSE trial included in company's naïve comparison vs. trifluridine-tipiracil

As no trial was found that reported treatment outcomes for trifluridine-tipiracil among patients with BRAF V600E mutant mCRC, the company used data from the intervention arm of the RECOURSE trial.[35] In the RECOURSE trial trifluridine-tipiracil was compared with placebo in patients with mCRC with unknown BRAF mutation status The company used this intervention arm data to carry out a naïve comparison against data for the intervention of interest for this STA (the encorafenib dual therapy arm of the BEACON trial). In the RECOURSE trial, KRAS mutation status was tested for all patients before trial enrolment and randomisation was stratified according to KRAS wild-type or mutant status. While patients' BRAF mutation status was unknown, the company cited a previous study suggesting that BRAF mutations occur in about 10% of KRAS wild-type mCRC.[36] As 51% of the trial population had KRAS wild-type mCRC, only around 5% of patients in the RECOURSE trial might have BRAF mutant mCRC as the company estimated (CS Document B, Section B.2.10.5, page 67). The generalisability of findings from this trial to the population of interest for this STA is therefore very limited. Since patients with BRAF mutant mCRC generally have much worse prognosis compared with other patients without the mutation among the KRAS wild-type mCRC group, the company 'adjusted for' the survival data from the RECOURSE trial. They applied a hazard ratio for BRAF wild-type vs BRAF mutant for OS and PFS obtained from the Peeters 2010/15 trial to produce estimated survival for patients with BRAF mutations treated with trifluridine-tipiracil before the naïve comparison with the BEACON trial encorafenib dual therapy arm.

Only data from the trifluridine-tipiracil arm of the RECOURSE trial was used in the naïve comparison against the dual therapy arm from the BEACON trial. Therefore the ERG's critique focuses on the comparability of the patient populations between the two trials (apart from the obvious discrepancy with respect to BRAF mutations). Selected baseline characteristics of participants are presented in Table 7 below. While the trial populations were similar with respect to age and ECOG performance status, the data clearly show that patients in the RECOURSE trial were much more treatment refractory. Whilst over 60% of patients had had four or more prior therapies in the RECOURSE trial, 66% of patients in the BEACON trial had received only one prior systemic therapy. Prior use of anti-EGFR was an exclusion criterion for the BEACON trial, whereas more than half of the patients in the RECOURSE trial had been treated with an anti-EGFR at baseline. Consequently, the ERG considers that the trial populations were too different for indirect comparisons to be made and that using data from these two trials is likely to generate results that are unlikely to be valid. Even if taken at face value, the company's naïve comparison would likely to be biased in favour of encorafenib dual therapy due to the substantial difference in treatment history between the patients. Therefore the ERG concludes that there is insufficient data to support a reliable comparison between encorafenib dual therapy and trifluridine-tipiracil. In addition, as highlighted earlier in Section 2.3 trifluridine-tipiracil may not be a suitable comparator for the proposed place in the treatment pathway suggested for encorafenib dual therapy.

Table 7. Comparison of selected baseline characteristics of participants in the BEACON and RECOURSE trials

Baseline characteristics	BEACON		RECOURSE	
	BEACON Ctrl (n=221)	**ENCO+c (n=220)**	**T&T (n=534)**	Placebo (n=266)
Age (years), median (range)	60 (27-91)	**61 (30-91)**	**63 (27-82)**	63 (27-82)
Female, N (%)	127 (58%)	**105 (48%)**	**208 (39%)**	101 (38%)
ECOG performance status				
0	108 (49%)	**112 (51%)**	**301 (56%)**	147 (55%)
1	113 (51%)	**104 (47%)**	**233 (44%)**	119 (45%)
2	0 (0%)	**4 (2%)**	**0 (0%)**	0 (0%)
Number of prior regimens				
1	145 (66%)	**146 (66%)**	**0 (0%)**	0 (0%)
2	75 (34%)	**74 (34%)**	**95 (18%)**	45 (17%)
3	1 (0.5%)	**0 (0%)**	**119 (22%)**	54 (20%)
4	0 (0%)	**0 (0%)**	**320 (60%)**	167 (63%)
Prior anti-EGFR	0 (0%)	**0 (0%)**	**278 (52%)**	144 (54%)

BEACON Ctrl: cetuximab plus FOLFIRI or irinotecan; ENCO+c: encorafenib + cetuximab; T&T: trifluridine-tipiracil

3.4 Critique of the indirect treatment comparison (ITC)

In the absence of a connected network, the company chose to combine the treatment nodes of the BEACON CRC trial control arm (cetuximab plus either FOLFIRI or irinotecan) with the experimental arm of the Peeters et al. 2010/2015 trial (FOLFIRI with panitumumab) for the post-hoc defined subgroup of 45 BRAF-mutant patients by assuming the following: a) equivalence between FOLFIRI and irinotecan and b) equivalence between cetuximab and panitumumab:

a) The assumption of equivalence between FOLFIRI and irinotecan was supported by previous empirical evidence from two trials that compared irinotecan to FOLFIRI on PFS and OS, showing statistically non-significant differences between the two therapies (Clarke et al., 2011 and Graeven et al., 2007).[37, 38]
b) The assumption of equivalence between cetuximab and panitumumab was assumed since both drugs belong to the same class, i.e. EGFR inhibitors.

The efficacy results (direct estimates of OS and PFS with 95% CIs) of BEACON CRC and Peeters et al. 2010/2015 trials along with the estimates of ITC between encorafenib with cetuximab vs. FOLFIRI are provided in Table 8. The ITC findings suggested a significantly improved OS (HR=0.39, 95% CI: 0.19, 0.81) and PFS (HR=0.30, 95% CI: 0.14, 0.68) with encorafenib plus cetuximab compared with FOLFIRI.

Table 8. Results from the company's Indirect Treatment Comparison (ITC)

Study	OS (HR)	PFS (HR)	
BEACON CRC trial	Enco + Cetu vs. (FOLFIRI or irinotecan) + Cetu		
	0.61 (0.48, 0.77)	0.44 (0.35, 0.55)	Direct comparison
Peeters et al. 2010/2015	FOLFIRI + Pani vs. FOLFIRI		
	0.64 (0.32, 1.28)	0.69 (0.32, 1.49)	Direct comparison
	Enco + Cetu vs. FOLFIRI		
BEACON CRC Peeters et al. 2010/2015	0.39 (0.19, 0.81)	0.30 (0.14, 0.68)	Indirect comparison
OS=overall survival; PFS=progression-free survival; cetu=cetuximab; pani=panitumumab; enco=encorafenib			

Key points from ERG's critique of the ITC include:

- The authors of the Peeters 2010/2015 study did not report baseline characteristics for the BRAF mutation subgroup of patients, which constituted of only ~ 10% (n=45) of the total sample (n=421). In the absence of this information it is not possible to properly assess the comparability of the patient populations between this trial and the BEACON CRC. The ERG was also unable to properly assess the RoB of the Peeters 2010/2015 trial due to the inadequacy of reporting of its methods
- In the ITC, the company combined two nodes to form an anchor (i.e., common comparator): one from the BEACON CRC study (FOLFIRI or irinotecan + cetuximab) and one from the Peeters et al. 2010/2015 study (FOLFIRI + panitumumab) to indirectly compare encorafenib dual therapy to FOLFIRI. This pooling requires two key assumptions (equivalence between FOLFIRI and irinotecan, and between cetuximab and panitumumab) which were only supported by data from small trials (trial subgroups) that showed inconsistent findings with low statistical power (see ERG's additional work described in Section 3.5.2 below). In addition, the assumptions introduce further levels of 'indirectness' of the evidence in addition to the inherent indirectness of evidence from ITC
- While the reported estimates of OS (HR=0.64, 95% CI: 0.32, 1.28) and PFS (HR=0.69, 95% CI: 0.32, 1.49) from the Peeters 2010/2015 trial suggested substantial survival benefit for adding panitumumab (and by extension, cetuximab according to the company's assumption) to FOLFIRI compared with FOLFIRI alone, these analyses were very under-powered. The presumed substantial effects of panitumumab based on the point estimates are also incongruent with other evidence and consensus reported in the literature, which suggest little benefit of anti-EGFRs in this group of patients (see Section 3.5.2.2 below)
- Given the indirectness, inconsistency and lack of precision in the evidence underpinning the company's ITC and its required assumption, the ERG concludes that estimates produced by the ITC were not reliable to form the basis of cost-effectiveness analysis.

3.5 Additional work on clinical effectiveness undertaken by the ERG

3.5.1 Verification of literature search

The ERG undertook additional literature searches (reported in detail in Appendix 1 on page 123) for potentially relevant clinical effectiveness studies using Google Scholar but did not identify additional studies that could have contributed to an NMA or ITC.

3.5.2 Verification of assumptions for ITC

As described in Section 3.4, two major assumptions are required to enable the connection between evidence from the BEACON CRC trial and trial evidence related to comparators specified in the final scope:

(1) Equivalence between FOLFIRI and single agent irinotecan.

(2) Equivalence between cetuximab and panitumumab.

Given the importance of these assumptions on the validity of the ITC, the ERG attempts to test these assumptions through triangulation of various sources of evidence, as described below.

3.5.2.1 Equivalence between FOLFIRI and irinotecan

Evidence cited by the company to support this assumption came from two relatively small head-to-head RCTs in which FOLFIRI was directly compared with irinotecan as the second-line treatment in mCRC patients in whom BRAF status was not established.[37, 38] The company stated that treatment groups did not differ significantly in OS or PFS (CS Document B, page 63) but did not present further details. EGR examined these two trials in further detail and their key characteristics and findings are summarised in Table 9 below.

Authors of one of the trials (DaVINCI) also reported a systematic review of additional 29 trials, which included a trial arm with irinotecan used as a second-line treatments either alone or in a combination regimen (i.e., FOLFIRI). Only very limited details were reported for the systematic review, and no critical appraisal of the included studies was reported. The authors highlighted that analyses were hampered by substantial variation in doses and schedules used for irinotecan-based regimens. Overall the findings suggest similar effectiveness between FOLFIRI and irinotecan, but highlight significantly lower risk of grade 3 or 4 diarrhoea for FOLFIRI compared with irinotecan (Odds ratio 0.45, 0.27 to 0.75 from meta-analysis of three RCTs; 8.4% [6 study arms, n=468] vs.23.5% [24 study arms, n=4201] from non-randomised comparison using data from all studies including single-arm trials).

Given the general prevalence of BRAF mutation of around 10% in CRC population,[6, 7] the generalisability of findings from the above two trials to the BRAF mutant population may be limited particularly in terms of clinical effectiveness. The ERG therefore seeks further evidence obtained from the specific population of interest to this STA. The ERG requested (in its clarification questions to the company) further data from the control group of the BEACON CRC trial, split by whether the patients received FOLFIRI with cetuximab or irinotecan with cetuximab. The re-constructed survival curves based on the data supplied by the company (CR Question A1) are shown in Figure 1 and Figure 2.

Table 9. Key features and findings of two head-to-head RCTs that have compared FOLFIRI with irinotecan as second-line treatment in mCRC

	Graeven et al., 2007[38]	DaVINCI, Clarke et al., 2011[37]
FOLFIRI regimen	Irinotecan 80 mg/m^2 followed by folinic acid 500 mg/m^2 and 5-FU 2,000 mg/m^2 24 h weekly for 6 weeks, with courses repeated on day 50 (7-week cycle), n=28	Irinotecan (180 mg/m^2 IV over 90 min, day 1), 5-fluorouracil (400 mg/m^2 IV bolus and 2400 mg/m^2 by 46-hour infusion from day 1) and folinic acid (20 mg/m^2 IV bolus, day 1), 2-weekly, n=44
Irinotecan single agent	Irinotecan 125 mg/m^2 weekly for 4 weeks, with cycles repeated on day 43 (6-week cycle), n=27	Irinotecan 350 mg/m^2 IV over 90 min, 3-weekly, n=45
Prior treatment with irinotecan	Not allowed	Not allowed
OS median (95% CI), months	FOLFIRI 9.5 (6.5 to 12.6) Irinotecan 10.7 (8.0 to 12.9)	FOLFIRI 15.4 (8.1 to 19.3) Irinotecan 11.2 (8.3 to 13.3) HR 0.72 (0.46 to 1.12)
PFS median (95% CI), months	FOLFIRI 3.7 (3.1 to 7.8) Irinotecan 3.7 (2.7 to 5.2)	FOLFIRI 6.2 (5.4 to 6.7) Irinotecan 4.0 (2.7 to 5.7) HR 0.81 (0.52 to 1.25)
Response rate	FOLFIRI 11% Irinotecan 11%	FOLFIRI 11% (4% to 25%) Irinotecan 11% (4% to 25%)
1-year survival	FOLFIRI 37% Irinotecan 42%	NR NR
Grade 3 to 4 adverse events Leukopenia Neutropenia Diarrhoea	 FOLFIRI 2/28 (7%) Irinotecan 5/27 (19%) FOLFIRI 0/28 (0%) Irinotecan 7/27 (26%) FOLFIRI 3/28 (11%) Irinotecan 5/27 (19%)	 NR NR FOLFIRI 7/42 (17%) Irinotecan 5/43 (12%) FOLFIRI 9.5% Irinotecan 18.6%

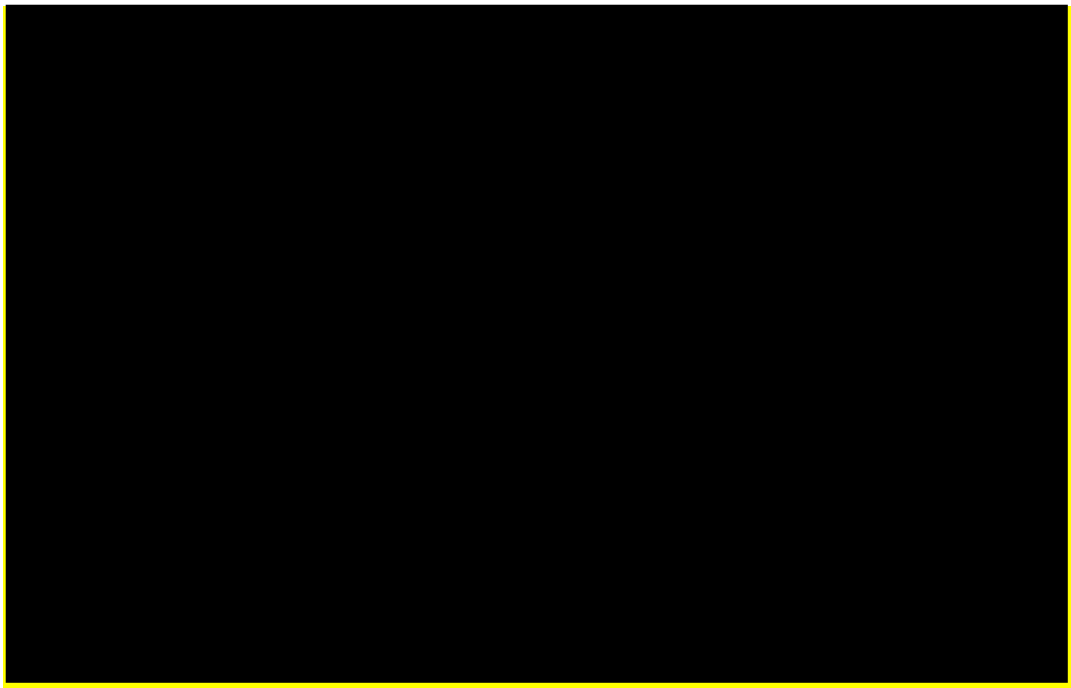

Figure 1. OS for the intervention and control arms of the BEACON CRC trial, showing break-down of the control arm by whether patients received FOLFIRI or irinotecan with cetuximab

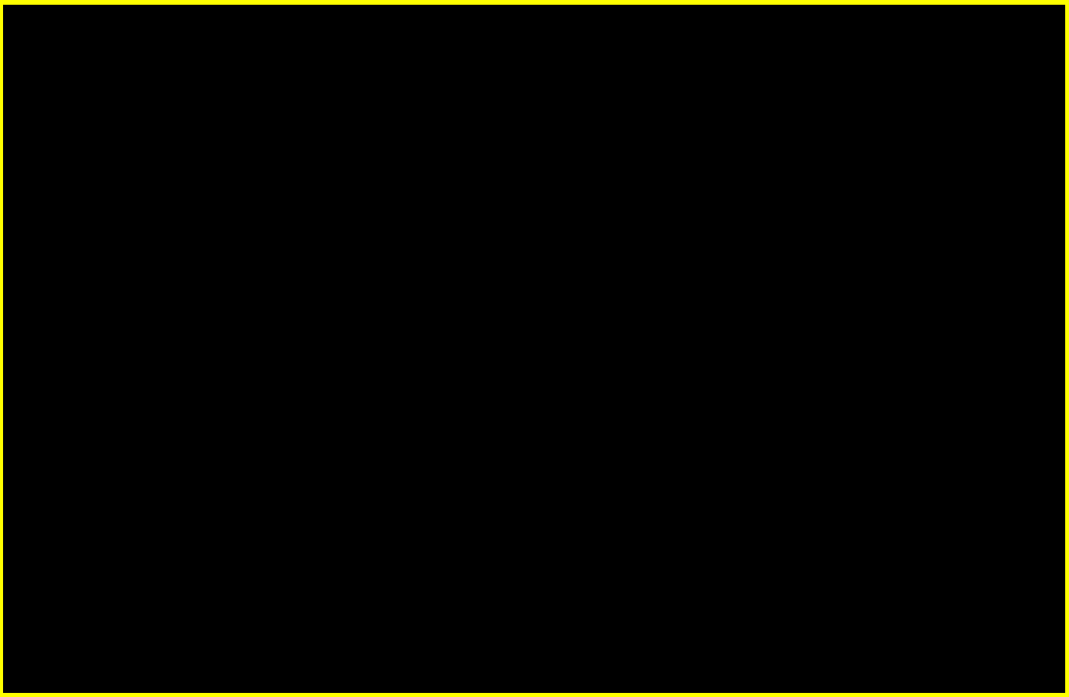

Figure 2. PFS for the intervention and control arms of the BEACON CRC trial, showing break-down of the control arm by whether patients received FOLFIRI or irinotecan with cetuximab

For OS,

For PFS,

[redacted]The results were [redacted] The ERG acknowledges that the comparisons were not randomised since patients received FOLFIRI or irinotecan depending on the choice of their treating physician in the trial. In fact the company gave the ERG data to show that there were substantial differences between patients treated with FOLFIRI plus cetuximab and irinotecan plus cetuximab (CR Question A1, Table 1), including [redacted] In addition, the trial would not have been sufficiently powered for comparisons between these two control options. The above data therefore only serve as a check for the potential existence of significant differences, which would raise concerns for the equivalence assumption.

Taken in the round, evidence from the literature and the BEACON trial does not suggest significant difference between FOLFIRI and irinotecan in terms of prolonging survival and slowing disease progression, although this is based on evidence for the mCRC population as a whole. The only evidence specific to the population with BRAF mutation is restricted to non-randomised comparisons within the BEACON CRC control group. However, it is clear from the literature that irinotecan single agent therapy is associated with a significantly higher risk of severe diarrhoea compared with FOLFIRI. Diarrhoea is an important adverse event that affects patient's tolerance of treatment. There is further concern that this adverse event can be aggravated by concomitant use of an anti-EGFR such as cetuximab (for which severe diarrhoea is one of the major adverse events affecting treatment tolerability).

3.5.2.2 Equivalence between cetuximab and panitumumab

The rationale cited by the company for this equivalence assumption includes that the mechanism of action is through inhibition of EGFR for both drugs and that NICE stated in TA439 that these drugs were likely to have similar effectiveness in treating RAS wild-type mCRC (CS Document B, page 63). While these are reasonable arguments, the key issue is whether the quoted evidence is generalisable to mCRC patients with BRAF V600E mutations – a subgroup of patients within the RAS wild-type mCRC population that is considered to have a poor response to anti-EGFR therapy.[13]

The company SLR did not identify any RCTs directly comparing cetuximab with panitumumab. The ERG is also not aware of direct comparison evidence between these two drugs in the BRAF V600E mutant population. However, while carrying out mapping of available evidence, the ERG identified

an opportunity for potential ITC through subgroup data available from three trials included in the company SLR (see lower-right part of Figure 3). Nevertheless given the small number of patients (total n=45 for the three trials), such an ITC is unlikely to be informative.

In the absence of direct comparative evidence between cetuximab and panitumumab in the population of interest, the ERG further considered broader literature concerning the effectiveness of anti-EGFRs in previously treated patients with BRAF mutant mCRC. Two systematic reviews were identified; [39, 40] neither showed statistically significant benefit for anti-EGFRs in a BRAF mutant mCRC population overall (i.e. including previously untreated mCRC). Only one of the reviews included meta-analyses for previous treated BRAF mutant mCRC. [39] The meta-analyses were based on three RCTs (total n=123). The pooled results did not suggest a significant treatment effect (HR 1.06, 95% CI 0.48 to 2.36 for OS; HR 0.84, 0.46 to 1.51 for PFS), although the analyses were under-powered.

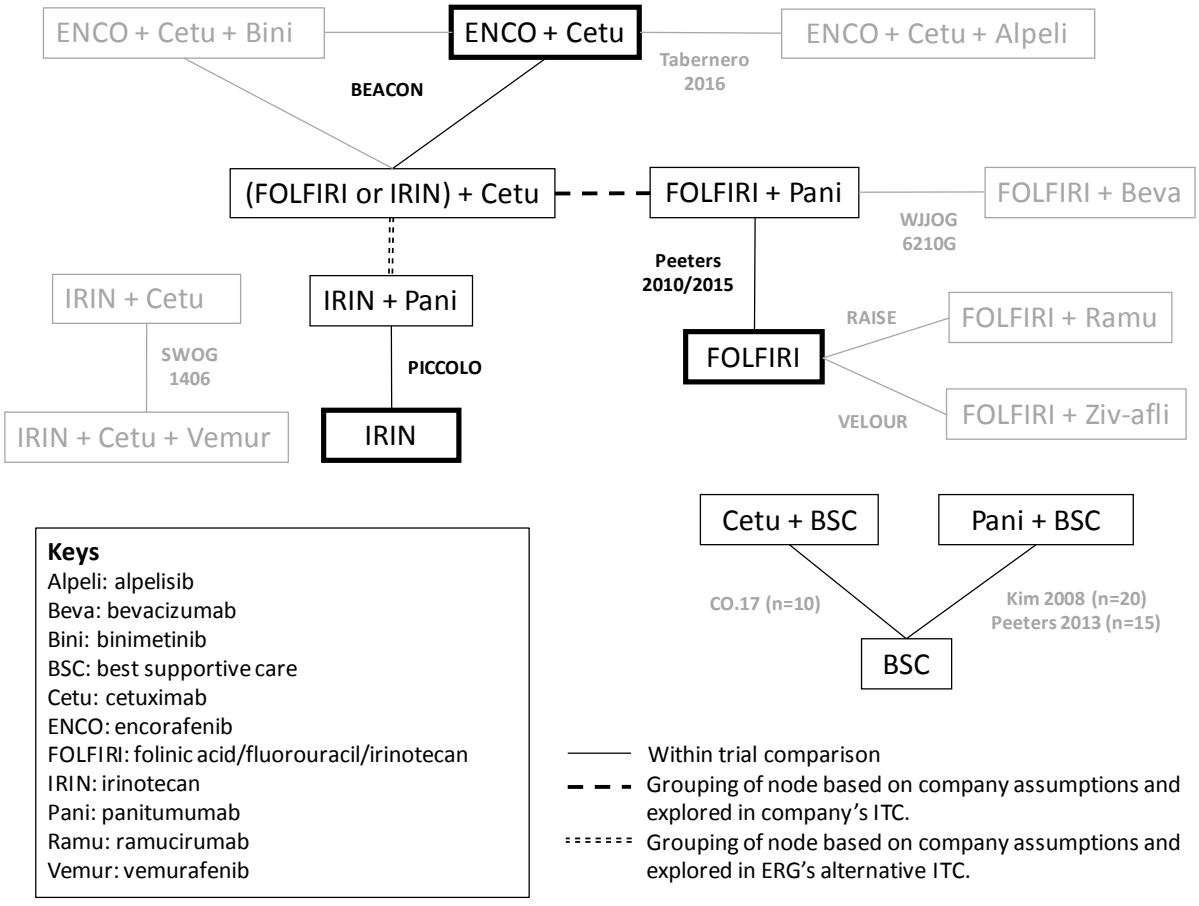

Figure 3. ERG's mapping of evidence network for RCTs conducted in patients with BRAF V600E mutations

3.5.3 Exploration of an alternative option for ITC

The ERG's mapping of RCT evidence above identified another potential ITC, through which encorafenib with cetuximab can be compared against single agent irinotecan, which is a comparator included in NICE final scope but excluded in the company submission. This ITC requires the same assumptions (i.e., equivalence between cetuximab and panitumumab, and between FOLFIRI and irinotecan) as those required for the company's ITC for comparing encorafenib with cetuximab against FOLFIRI. As illustrated by the double-dashed line in Figure 3, the same assumptions allow grouping of the control arm of the BEACON CRC trial with the panitumumab plus irinotecan arm in the PICCOLO trial [32] to create a grouped treatment node, through which comparison with single agent irinotecan can be made.

The PICCOLO trial was an open-label RCT conducted across 60 centres in the UK in patients who had advanced CRC progressing after fluoropyrimidine treatment with or without oxaliplatin. Three treatments were compared in the trial: irinotecan plus panitumumab, irinotecan plus ciclosporin, and irinotecan (single agent). The irinotecan plus ciclosporin arm is not relevant for this STA and therefore will not be described further. The trial initially recruited and randomised molecularly unselected patients (i.e., without considering genetic mutations), but the trial protocol was formally modified and the trial was re-launched with full prospective molecular stratification in view of emerging evidence associating KRAS mutation with treatment response for anti-EGFR therapy.[32] Panitumumab randomisation was restricted to KRAS wild-type patients following the re-launch. The publication cited here[32] presents the randomised comparison between irinotecan plus panitumumab (n=230) and irinotecan (n=230) in patients with KRAS wild-type, taking into account the study design. BRAF mutations were identified in 37 and 31 patients in each of the arms respectively.

The characteristics of patients with BRAF mutations were not separately reported. Compared with the BEACON CRC trial, the overall patient population included in this PICCOLO trial analysis was slightly older (by 2-3 years), with a higher proportion of males (approximately 70% vs. just under 50%) and a higher proportion of patients who had had their primary tumour resected (approximately 75% vs. 55%). One major difference between the trial populations was that patients in the PICCOLO trial were irinotecan naïve whereas approximately [redacted] in the BEACON CRC had prior irinotecan treatment.

Patients with BRAF mutations in the PICCOLO trial who were treated with irinotecan plus panitumumab had significantly *worse* OS (HR 1.84, 95% CI 1.10 to 3.08) compared with those treated with irinotecan alone. There was no significant difference between the two arms in PFS (HR 1.40, 95% CI 0.82 to 2.39). Linking these findings with the findings from BEACAN CRC through the grouped node generated by the two aforementioned assumptions, the results of ITC suggested no

significant difference between encorafenib plus cetuximab and irinotecan, with OS in favour of irinotecan and PFS in favour of encorafenib plus cetuximab (see Table 10).
Given the differences in patient population between the two trials and the relative small number of patients with BRAF mutations in the PICCOLO trial, these findings should be treated with great caution. Nevertheless, the findings highlight the substantial uncertainties associated with assumptions required for ITCs included in this STA and their resultant estimates.

Table 10. Results from the ERG's additional ITC

Study	OS (HR)	PFS (HR)	Comparison
BEACON CRC	Enco + Cetu vs. (FOLFIRI or irinotecan) + Cetu		
	0.61 (0.48, 0.77)	0.44 (0.35, 0.55)	Direct comparison
PICCOLO	Irinotecan + Pani vs. irinotecan		
	1.84 (1.10, 3.08)	1.40 (0.82, 2.39)	Direct comparison
	Enco + Cetu vs. irinotecan		
ITC	1.12 (0.64, 1.98)	0.62 (0.34, 1.10)	Indirect comparison
OS=overall survival; PFS=progression-free survival; cetu=cetuximab; pani=panitumumab; enco=encorafenib			

3.5.4 Survival for patients with BRAF V600E mutant mCRC

Data for OS were not sufficiently mature for the BEACON CRC trial at the data cut-off time of August 2019 reported in the CS, with [redacted] of the patients still being followed for survival (CS Document B Appendices Section D2.2, page 112). The ERG therefore compiled available survival data from other RCTs and observational studies conducted in previously treated patients with BRAF mutant mCRC, identified through the company's SLRs and the ERG's additional searches. These data are shown in Table 49 in Section 5.5 of this report and are used to guide the ERG's validation of modelling results for longer-term survival.

3.6 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence included in this CS primarily came from the pivotal BEACON CRC trial, in which encorafenib combined with cetuximab was compared with a control treatment of cetuximab combined with either FOLFIRI or irinotecan. Patients treated with encorafenib, combined with cetuximab, had significantly longer OS, PFS and time before a definitive 10% deterioration in HRQoL measures. They also had a higher overall response rate compared with control treatment.

The ERG identified potential risk of bias in several domains in the BEACON trial including lack of blinding and possible bias introduced by censoring due to unequal study withdrawal between treatment arms. These have the potential to impact the reliability of effect estimates from this trial.

A major complication in this assessment is that cetuximab was included in all trial arms of the BEACON CRC trial, including the control arm. As cetuximab is not recommended in the UK for treating mCRC beyond first line, the control arm (cetuximab combined with FOLFIRI or irinotecan) differs from the comparators (FOLFIRI or irinotecan without cetuximab) specified in the final scope. Consequently, there is no trial evidence that allows a direct comparison between the technology (encorafenib plus cetuximab) and appropriate comparators (FOLFIRI, irinotecan or trifluridine-tipiracil).

In view of lack of direct comparative evidence, the company carried out an ITC between encorafenib plus cetuximab and FOLFIRI using two major assumptions (equivalence between cetuximab and panitumumab, and between FOLFIRI and irinotecan). By making these two assumptions, evidence from the BEACON CRC study (encorafenib + cetuximab vs. FOLFIRI/irinotecan + cetuximab) can be connected to evidence from another trial (Peeters 2010/2015) in which FOLFIRI plus panitumumab was compared with FOLFIRI. However, evidence from the Peeters 2010/2015 trial was based on a subgroup of only 45 patients whose tumour was found to carry BRAF mutation. The trial therefore lacked statistical power. The estimated hazard ratios (HRs) from the trial for panitumumab plus FOLFIRI vs. FOLFIRI used in the ITC, while suggestive of a benefit for adding panitumumab (and by extension an anti-EGFR) to FOLFIRI compared with FOLFIRI alone, were not statistically significant (HR 0.64, 95% CI 0.32 to 1.28 for OS; HR 0.69, 95% CI: 0.32 to 1.49 for PFS). The impact of the adjustment made through the ITC based on these data would be likely to inflate the effectiveness of encorafenib dual therapy compared with FOLFIRI due to the presumed benefit of cetuximab/anti-EGFR in the BEACON control arm.

Contrary to the findings from the Peeters trial, the ERG notes that evidence from subgroup analysis among patients with BRAF mutant mCRC in another PICCOLO trial [32] suggested a potentially harmful effect for adding panitumumab to irinotecan compared with irinotecan alone (HR 1.84, 95% CI 1.10 to 3.08 for OS; HR 1.40, 95% CI 0.82 to 2.39). There is therefore inconsistency in evidence with regard to the effects of adding an anti-EGFR to an irinotecan-based therapy. The ERG carried out an alternative, exploratory ITC to compare encorafenib plus cetuximab with irinotecan using the same assumptions underlying the company's ITC through data from the PICCOLO trial. The exploratory ITC, while clearly lacking statistical power and subject to uncertain validity of the same assumptions, did not demonstrate clear benefit for encorafenib dual therapy over irinotecan.

Because of the indirectness, inconsistency and lack of precision in the evidence underlying the company's ITC, alongside violations of the transitivity assumption, the ERG considers that estimates from the ITC, which are used directly to inform the company's base case for cost-effectiveness analysis, are highly uncertain. Given the current evidence, there is actually no reliable source of data to furnish the comparison between encorafenib dual therapy and FOLFIRI as required in the NICE final scope. Taken into account all the issues highlighted above, the ERG considers the randomised comparison between the encorafenib dual therapy arm and the control arm of the BEACON CRC trial as the most suitable proxy for estimating the relative effectiveness of the technology compared with a comparator in which FOLFIRI is the preferred choice.

The effectiveness of trifluridine-tipiracil has not been evaluated in the population with BRAF V600E mutant mCRC. The company carried out a naïve comparison using data from the RECOURSE trial, which was undertaken in a population with unknown but likely very small proportion of patients with BRAF mutations. Furthermore, patients included in the RECOURSE trial were much more treatment refractory, and were therefore not comparable to the population in the BEACON CRC trial. Consequently the ERG concludes that there is lack of evidence to allow reliable comparison between encorafenib dual therapy and trifluridine-tipiracil. The ERG further notes that trifluridine-tipiracil is usually used as third- or subsequent line therapy. Therefore, while the company suggested that encorafenib dual therapy could replace trifluridine-tipiracil as a third-line therapy, the technology is most likely to be used as a second-line therapy in clinical practice and thus occupies an earlier place in the treatment pathway compared with trifluridine-tipiracil.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

4.1.1 Search strategy and study selection criteria

The company undertook a SLR "to summarise the available economic data for mCRC treatments." (CS Document B Appendices, page 119). Searches were undertaken in April 2019 and updated in November 2019. Appropriate databases (Medline, Embase, CRD HTA and NHS EED) were searched to identify economic studies published since 2009. However, as the CRD databases are no longer updated (HTA since 2018 and EED since 2015), some recent HTAs and economic evaluations may have been missed. Supplementary searches using internet search engines and/or websites of international HTA agencies and conferences would have been useful. No hand-searching was undertaken.

The CS states: "Keywords for population were combined with keywords for economic models" (CS Document B Appendices, page 119), and the SLR eligibility criteria (Table 15, CS Document B Appendices, page 131) indicate no restriction on the intervention/comparators. However, as well as population and economic keywords, the names of many specific cancer drugs are included in the search strategies, introducing a restriction on the comparators included. The ERG therefore considers the scope of the SLR to be unclear. Potentially useful cost effectiveness data in studies of pharmacological interventions 'in general' (that is, not mentioning specific drug names in the title, abstract or other indexed fields) and non-pharmacological treatments may have been missed or excluded from the SLR.

Health-Related Quality of Life

A separate SLR was undertaken to identify utility data for potential use in the model. An appropriate selection of databases was searched, as well as Google Scholar, and reference lists of included studies were hand-searched (CS Document B Appendices pages 133, 137). Some search concepts or terms related to utility values that may have identified additional studies were not used, e.g., QALYs (excluded from Embase only), DALYs, Standard gamble, Preference values, Disutility, FACT-G (General), Functional Assessment of Cancer Therapy. It is therefore possible that some potentially useful studies were missed.

The SLR inclusion criteria were narrowed post-hoc to studies of specific interventions (FOLFIRI or trifluridine-tipiracil) in previously treated mCRC, or studies specific to BRAF mutation patients. (CS Document B Appendices, pages 137-8; CS Document B, page 125).

4.1.2 Identified studies

The company identified 64 publications potentially eligible for the SLR (CS Document B Appendices, page 132). Although UK context was not listed in the eligibility criteria, only eight UK cost-effectiveness studies are considered further (CS Document B, page 91), of which four studies related to first line and the other four related to second or subsequent lines of treatments for mCRC. None of the studies concerns the BRAF V600E mutant population. Key methods and findings were tabulated (CS Document B, Table 20, pages 93-96) but no further comments were provided. The company also examined and listed key features of six prior economic analyses included in previous NICE technology appraisals (CS Document B, Table 22, page 101).

In view of the potential issues in literature search identified above, the ERG undertook three additional searches of health technology assessment reports and cost-effectiveness studies through Google on 25th March 2020 (see Appendix 2 on page 123). After comparison with the company's included and excluded studies (CR Question A15, pages 154-169), we identified two studies that had not been found by the company and appeared to meet the eligibility criteria.[41, 42] However no information relevant to this STA was covered in these studies.

4.1.3 Interpretation of company cost-effectiveness SLR

Overall the cost-effectiveness SLR seems to have identified key economic literature relevant to treatments of mCRC despite some issues related to searches. Similarly to the clinical effectiveness evidence, there is paucity of literature that specifically examines the cost-effectiveness of treatments for BRAF V600E mutant mCRC. Consequently, while the company SLR only listed key features of a few most relevant studies without undertaking future critique of this evidence, the ERG considers it a reasonable approach. The identification and comparison of economic analyses used in previous NICE technology appraisals to justify the company's modelling approach is a merit.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

Due to the ERG's view that the naïve comparison with trifluridine + tipiracil is largely invalid, in what follows the comparison with trifluridine + tipiracil is not dwelt upon. The details of the company approach for this comparison are given in Appendix 3, though the company cost effectiveness results for the comparison of encorafenib + cetuximab with trifluridine + tipiracil are presented in Chapter 5. The ERG concentrates upon the comparison with FOLFIRI, and produces an ERG revised base case only for this comparison.

4.2.1 NICE reference case checklist

Table 11. 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	Yes. But the ERG thinks that due to the naïve comparison with trifluridine + tipiracil, pairwise comparisons with the comparators are more informative
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	10 years: sufficient to account for the vast majority of overall survival (OS)
Synthesis of evidence on health effects	Based on systematic review	Yes
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	BEACON EQ-5D data is used
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, the UK social tariff is applied

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
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure, assumptions and input summary

The company presents a standard partitioned survival model with the three health states of progression free survival (PFS), post progression survival (PPS) and dead. The company compares encorafenib + cetuximab with FOLFIRI and with trifluridine + tipiracil. The model applies a monthly cycle and has a 10 year time horizon, which is sufficient to account for the vast majority of overall survival (OS).

For encorafenib + cetuximab the company fits parameterised OS and PFS curves to the BEACON trial encorafenib + cetuximab arm data. The company applies the log-logistic curves for its base case following assessment of the information criteria.

The BEACON control arm is not modelled in the company base case, due to it including cetuximab. For FOLFIRI the company applies the hazard ratios of its ITC, 2.56 for OS and 3.33 for PFS, to the encorafenib + cetuximab log-logistic curves.

For trifluridine + tipiracil that company fits OS and PFS parameterised curves to RECOURSE trial data. These are further conditioned by BRAF V600 to BRAF wild type hazard ratios, 4.00 for OS and 3.57 for PFS. There is no link from the trifluridine + tipiracil to the encorafenib + cetuximab, so the company performs a naïve comparison.

Time on treatment is not separately modelled, but is assumed to be the same as PFS.

Arm-specific quality of life values for PFS and PPS are taken from the BEACON trial EQ-5D data, with those of the control arm being applied to FOLFIRI. The quality of life values for trifluridine + tipiracil are assumed to be the average of those of encorafenib + cetuximab and FOLFIRI. The PPS quality of life values are the average of the end of treatment values and the 30 day follow-up values, and are assumed to apply through PPS.

Adverse events are included but only affect costs due to it being assumed that their effect upon quality of life is within the BEACON trial EQ-5D data.

The direct drug costs for intravenously administered treatments have relative dose intensities applied, taken from the BEACON trial. Ongoing PFS administration and follow-up costs are applied, FOLFIRI require additional resource use for peripherally inserted central catheter (PICC) line maintenance. Ongoing PPS costs are the same across comparators.

For encorafenib + cetuximab and FOLFIRI, half of those moving into PPS are assumed to receive two months treatment with trifluridine + tipiracil. Those initially receiving trifluridine + tipiracil who move into PPS are assumed to receive no further treatment.

4.2.3 Model structure

The company presents a standard partitioned survival analysis with a monthly cycle length.

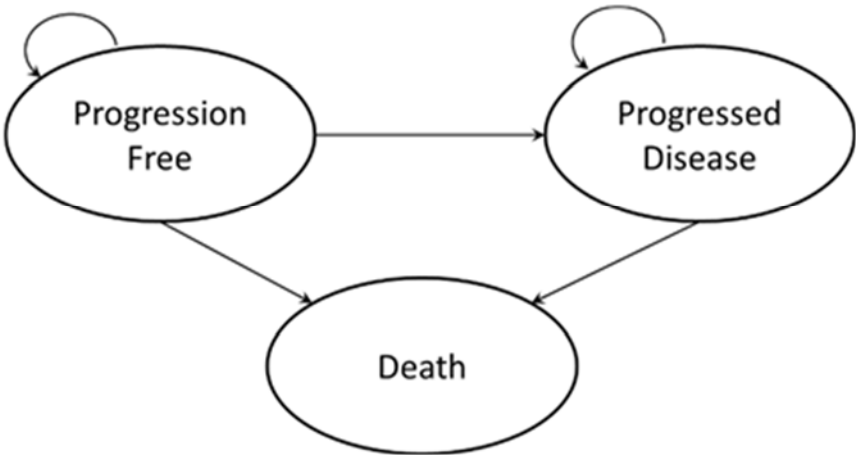

Figure 4. Company model structure (Reproduced from CS Document B, Figure 7, page 99)

All patients start the model in PFS. The proportion surviving over time is modelled using parameterised OS curves. This is then divided into patients in PFS and patients in post progression survival (PPS) using a parameterised PFS curve.

Time to treatment discontinuation (TTD) curves are not separately modelled. The company assumes that patients in PFS remain on their initial treatment; i.e. a treatment's TTD curve is the same as its PFS curve. Patients in PPS may receive a different treatment or may discontinue treatment altogether.

4.2.4 Population

The company models the patient population of the BEACON CRC trial: BRAF V600E mutant mCRC patients who have failed at least one prior treatment.

4.2.5 Interventions and comparators

The company models three possible initial treatments for those in PFS:

- Encorafenib + cetuximab (ENCO+c);
- FOLFIRI: folinic acid + fluorouracil + irinotecan; and,
- Trifluridine + tipiracil (T&T).

The company assumes that of those who received encorafenib + cetuximab during their PFS and those who received FOLFIRI during their PFS, half would receive trifluridine + tipiracil during their PPS.

4.2.6 Perspective, time horizon and discounting

The perspective and discounting are as per the NICE reference case. A time horizon of 10 years is applied. For the company base case, the proportions of patients modelled as remaining alive at 10 years are:

- 1.4% for encorafenib + cetuximab,
- 0.0% for FOLFIRI, and
- 0.0% for trifluridine + tipiracil

4.2.7 Treatment effectiveness and extrapolation

The main clinical effects are estimated as follows:

- For encorafenib + cetuximab the company estimates parameterised OS and PFS curves from the BEACON trial encorafenib + cetuximab Kaplan Meier data. Based upon the information criteria the company applies and extrapolates using the log-logistic curve for both OS and PFS.
- For the FOLFIRI OS and PFS curves, the company applies its ITC hazard ratios of 2.56 for OS and 3.33 for PFS to the encorafenib + cetuximab log-logistic OS and PFS curves.

Grade 3+ adverse events rates are taken from the single treatment arms of the relevant three trials. These have no effect upon patient quality of life due to an assumption that the BEACON PFS quality of life values that are applied include these effects. Adverse events only affect costs, these mainly increasing for FOLFIRI, due to its higher rates of neutropenia, leukopenia and liver failure.

The details of this are presented in sections 4.2.7.1 to 4.2.7.6 below. If the above summary is sufficient, readers may wish to turn to section 4.2.8 on page 75 which summarises the quality of life data.

4.2.7.1 Treatment effectiveness: Encorafenib + cetuximab

The company fits parameterised curves to the BEACON encorafenib + cetuximab, with the following information criteria.

Table 12. BEACON encorafenib + cetuximab arm: parameterised curves' information criteria

	OS		PFS	
Curve	AIC	BIC	AIC	BIC
Exponential	946.6	950.0	960.9	964.3
Weibull	937.7	944.5	936.6	943.3
Gompertz	946.4	953.2	956.8	963.6
Log-normal	934.9	941.7	924.2	931.0
Gamma	934.0	944.2	924.4	934.6
Log-logistic	**929.4**	**936.2**	**920.5**	**927.3**

For their base case the company selects the log-logistic for both OS and PFS due to it having the lowest AIC and BIC. The ERG presents the parameterised curves below, alongside the BEACON Kaplan Meier curves and number at risk in Figure 5 and Figure 6 below.

Figure 5. Company OS curves and KM data: BEACON encorafenib + cetuximab arm

The shape of the Kaplan Meier S(t) curve makes it difficult for any of the smoothly evolving smooth parameterised curves to fit particularly precisely. The parameterised curves show some initial divergence, then a coming together around month 9 before beginning to diverge again.

While admittedly arbitrary, by month 16 only 10% of patients remain at risk with the OS KM S(t) being somewhat above this at 34%. Given the limited number of patients remaining at risk post 16 months, the ERG uses this 16-month data cut-off for its analysis of the areas under the parameterised OS curves.

Figure 6. Company PFS curves and KM data: BEACON encorafenib + cetuximab arm

The parameterised curves when extrapolated over the model time horizon are presented in Figure 7 and Figure 8 below.

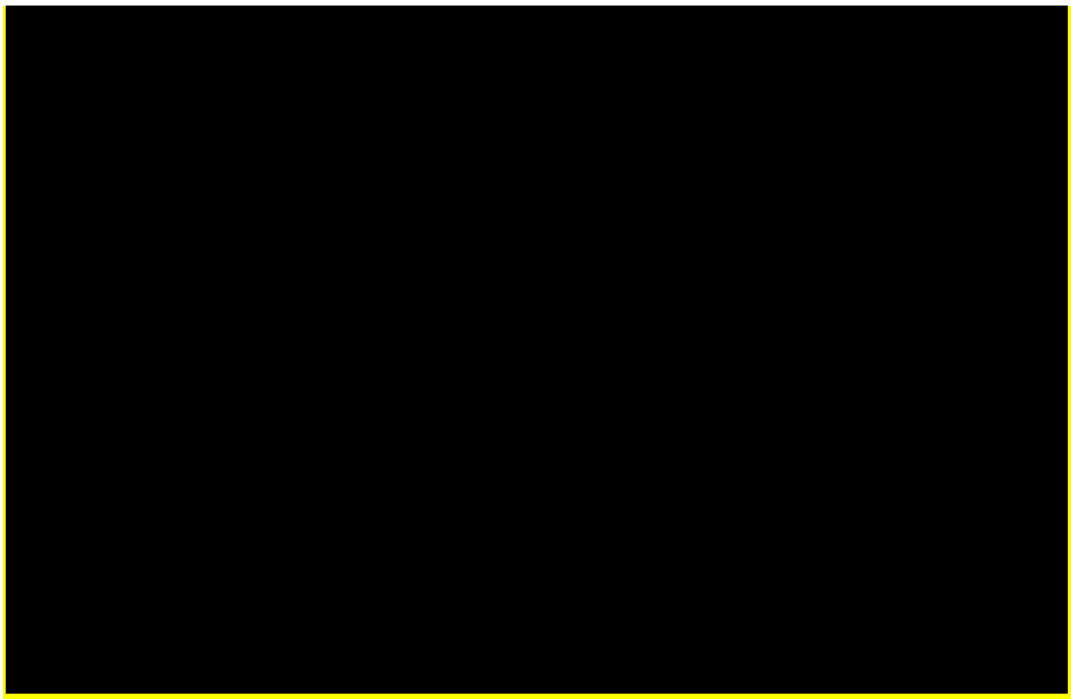

Figure 7. Company OS curves extrapolated

During the period of extrapolation, the log-logistic and log-normal OS curves rise above the other curves. As is usual, the log-logistic and log-normal curves have considerably longer tails than the

other parameterised curves. The Weibull, which is often applied within modelling of cancer survival, is the lowest curve from around 15 months.

Figure 8. Company PFS curves extrapolated

The PFS log-logistic curve is perhaps more closely aligned with the other parameterised curves than is the case for the OS curves. While it has a longer tail, the tail is relatively close to the horizontal axis and only a small percentage of patients; e.g. 0.76% at 48 months, are modelled as remaining progression free. Again, the Weibull is the lowest curve from around month 11.

The areas under the curves (AUCs), and the differences in these from the company base case log-logistic curves, to 16 months and to the model 10 year time horizon are presented in Table 13.

Table 13. Months AUCs: Encorafenib + cetuximab company parameterised curves

	OS		PFS	
Curve	16 Months	10 years	16 Months	10 years
Exponential				
Weibull				
Gompertz				
Log-normal				
Gamma				
Log-logistic				

The average months OS at 16 months is extremely similar between the parameterised curves, despite Figure 5 perhaps suggesting some differences between them. The divergence in estimates occurs during extrapolation, with both the log-normal and the log-logistic estimating somewhat longer average survival than the other curves. As would be expected, the average PFS estimates are more similar between the curves, at both 16 months and at 10 years.

4.2.7.2 Relative treatment effectiveness: FOLFIRI

The BEACON control arm informed the company ITC and resulting hazard ratio. But the company base case does not direct apply any of the Kaplan Meier data from the BEACON control arm or fit parameterised curves to this data, due to both FOLFIRI and irinotecan being used in conjunction with cetuximab. The company applies the company ITC hazard ratio estimates for FOLFIRI compared to encorafenib + cetuximab of 2.56 (1.23 – 5.26) for OS and 3.33 (1.47 – 7.14) for PFS. This results in the following areas under the curves.

Table 14. Months AUCs: FOLFIRI company base case

	OS		PFS	
Curve	16 months	10 years	16 months	10 years
Exponential	[redacted]			
Weibull				
Gompertz				
Log-normal				
Gamma				
Log-logistic				

4.2.7.3 Treatment effectiveness: FOLFIRI: BEACON control arm scenario analysis

The company model permits sensitivity analyses that apply company parameterised curve estimates from the BEACON trial control arm, the information criteria of which are presented in Table 15. It appears that these curves are estimated independently from those of the BEACON encorafenib + cetuximab arm presented in Section 4.2.7.1 above.

Table 15. BEACON control arm: parameterised curves' information criteria

	OS		PFS	
Curve	AIC	BIC	AIC	BIC
Exponential	1009.8	1013.2	642.6	646.0
Weibull	1004.6	1011.4	641.1	647.9
Gompertz	1010.3	1017.1	640.2	647.0
Log-normal	1012.3	1019.1	602.2	609.0
Gamma	1003.6	1013.8	604.1	614.3
Log-logistic	**1000.3**	**1007.1**	**588.6**	**595.4**

The company scenario analysis applies the log-logistic curve for both OS and PFS.

For its base case the company selects the log-logistic for both OS and PFS due to it having the lowest AIC and BIC. The ERG presents the parameterised curves below, alongside the BEACON Kaplan Meier curves and number at risk in Figure 9 and Figure 10 below.

Figure 9. Company OS curves and KM data: BEACON control arm

Much the same considerations apply as in the encorafenib + cetuximab arm, with the shape of the Kaplan Meier S(t) curve makes it difficult for any of the smoothly evolving smooth parameterised curves to fit it particularly precisely.

By month 14 only 10% of patients remain at risk with the OS KM S(t) being somewhat above this at 20%. The divergence between the number at risk and the OS KM S(t) proportion is less than in the encorafenib + cetuximab arm so there is an argument to extend beyond this point, and the ERG retains the 16-month cut-off for comparing the areas under the parameterised curves.

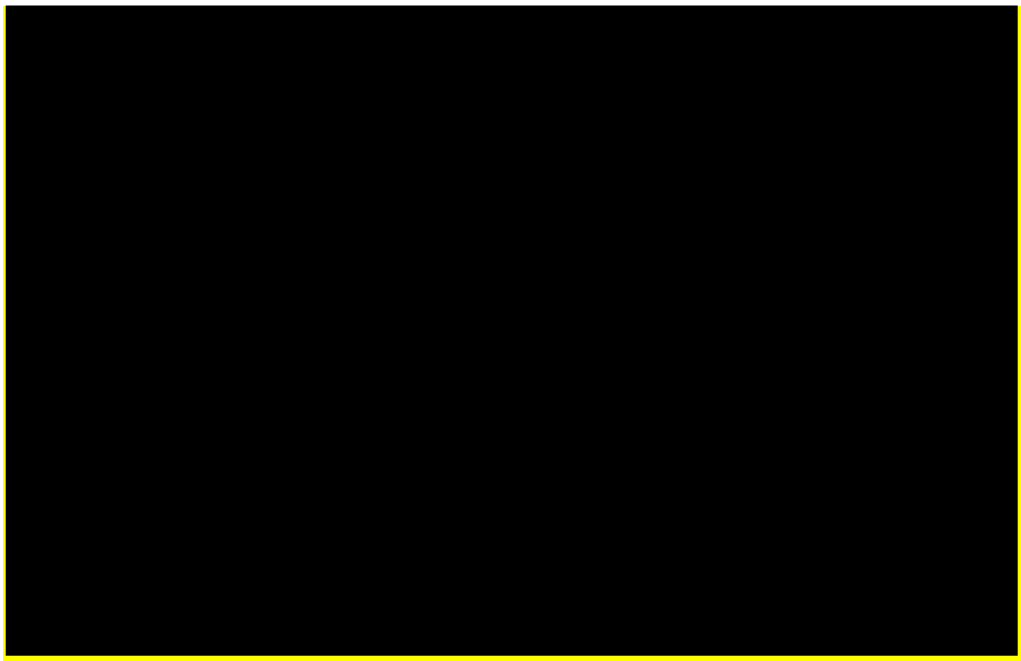

Figure 10. Company PFS curves and KM data: BEACON control arm

The shape of the control arm PFS Kaplan Meier S(t) curve makes it particularly challenging for the smooth parameterised curves to accurately represent. The experience of the first two or three months appears to be quite different from that thereafter, and none of the parameterised curves are a good visual fit. The log-logistic appears to be a particularly poor fit from month 2 onwards, though the numbers at risk are declining quite sharply from this point.

The parameterised curves when extrapolated over the model time horizon are presented in Figure 11 and Figure 12 below.

Figure 11. Company OS curves: BEACON control arm

As with the encorafenib + cetuximab arm, during the period of extrapolation the log-logistic and log-normal OS curves rise above the other curves and have longer tails than the other parameterised curves. The Weibull is the lowest curve from around 12 months.

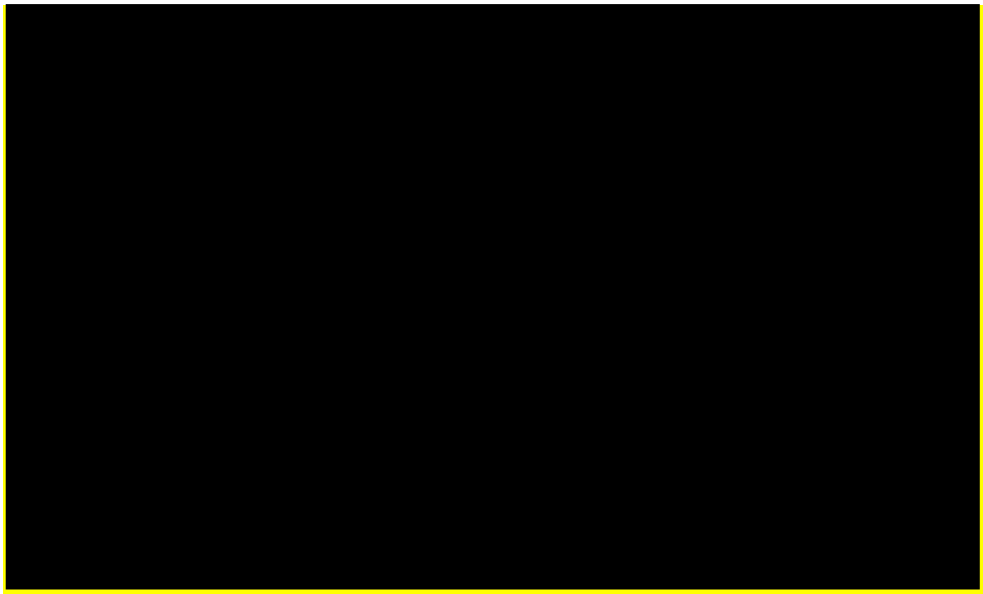

Figure 12. Company PFS curves: BEACON control arm

The PFS curves are more aligned with one another than the OS curves, though the Gompertz rises a bit above the others from around 6 months.

Within the BEACON KM data the numbers at risk remain reasonably aligned with the OS curve to around 16 months. The areas under the curves (AUCs), and the differences in these from the company base case log-logistic curves, to month 16 and to the model 10 year time horizon are presented in Table 16.

Table 16. Months AUCs: BEACON control arm company parameterised curves

	OS		PFS	
Curve	16 months	10 years	16 months	10 years
Exponential	[redacted]			
Weibull				
Gompertz				
Log-normal				
Gamma				
Log-logistic				

As with the encorafenib + cetuximab parameterised curves, for the control arm to month 16 there is little difference in either the average overall survival or the average PFS. The differences only emerge during extrapolation, with the log-normal and log-logistic predicting somewhat longer overall survival than the other parameterised curves.

4.2.7.4 Treatment effectiveness: All comparators' curves

The OS and PFS curves of the three comparators are graphed in Figure 13 and Figure 14 below, alongside the BEACON control arm curves and RECOURSE curves for completeness.

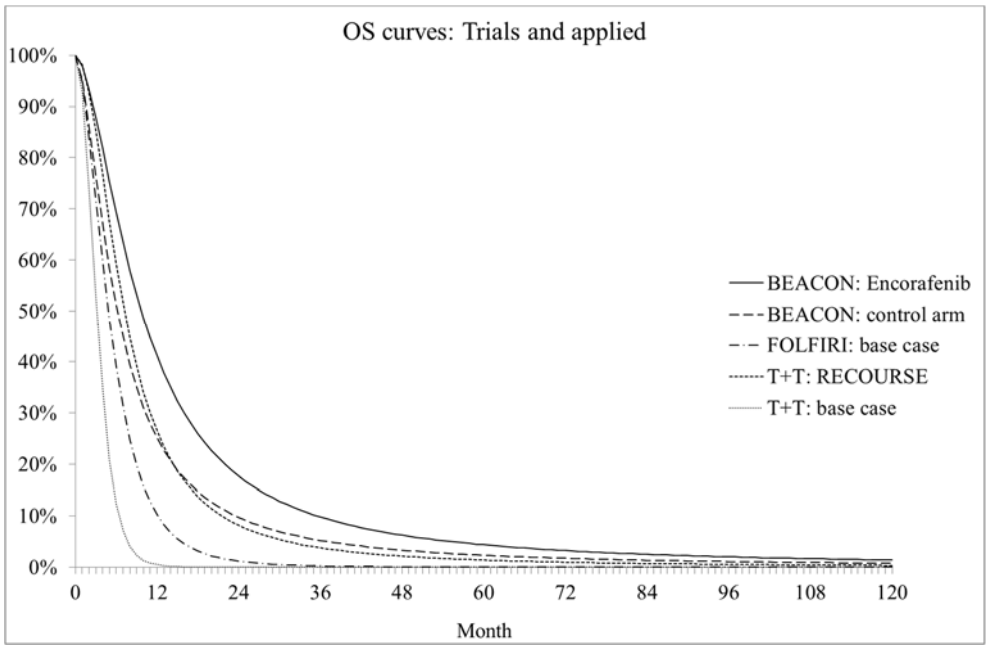

Figure 13. Company OS curves: All comparators

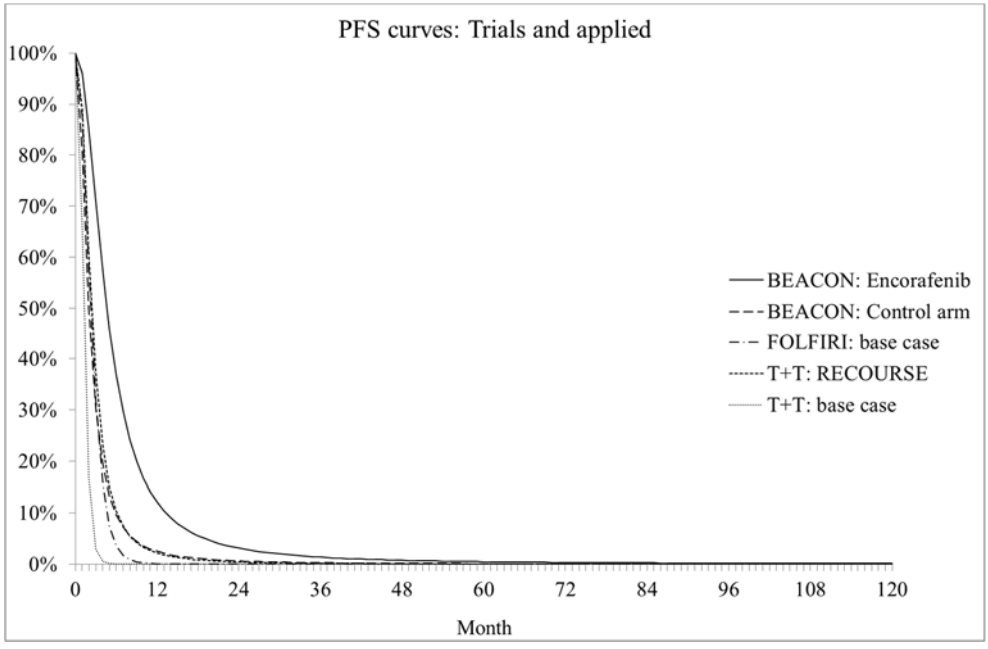

Figure 14. Company PFS curves: All comparators

The parameterised curves' total undiscounted months OS, PFS and PPS within the 10 year time horizon, and the net gain from encorafenib + cetuximab relative to the other comparators, are presented in Table 17 below.

Table 17. Undiscounted months OS, PFS and PPS

	Absolute months survival			Encorafenib months net gain		
Months	OS	PFS	PPS	OS	PFS	PPS
BEACON: Encorafenib	16.8	7.4	9.4	..	..	..
BEACON: Control arm	11.6	3.5	8.1	5.2	3.8	1.4
FOLFIRI: base case	6.6	3.1	3.6	10.1	4.3	5.9

Encorafenib + cetuximab is estimated to result in overall survival gains of 10.1 months compared to FOLFIRI. It is anticipated that the majority of the survival gains occurs after progression, when treatment with encorafenib + cetuximab is assumed to have stopped.

4.2.7.5 Treatment effectiveness: Time on treatment

The company presents the BEACON Kaplan Meier time to treatment discontinuation (TTD) plots alongside the KM PFS plots for encorafenib + cetuximab and the control arm in CS Document B Figures 16 and 17, on pages 120 and 121. These also include the 95% confidence intervals for the curves which overlap. The ERG presents the KM plots below in Figure 15 and Figure 16, based upon the data supplied in the second CR and Issue 4 response, and refers the reader to the CS Figures 16 and 17 for the 95% confidence intervals.

Figure 15. BEACON PFS and TTD KM curves: Encorafenib + cetuximab

Figure 16. BEACON PFS and TTD KM curves: Control arm

The planned monthly PFS assessments cause the encorafenib + cetuximab PFS curve to initially drop in steps, and these steps are initially replicated in the TTD. But after around month 5 the encorafenib + cetuximab TTD KM curve lies above the PFS KM curve.

The picture for the BEACON control arm is the reverse with the TTD curve typically lying below the PFS curve, but it may be that this is complicated by the control arm being composed of two regimens: FOLFIRI + cetuximab and irinotecan + cetuximab.

4.2.7.6 Treatment effectiveness: Adverse events

Adverse events are included but only affect costs, so are summarised in Section 4.2.9.4 below.

4.2.8 Health related quality of life

4.2.8.1 BEACON quality of life values: PFS and PPS

The company applies the average BEACON EQ-5D values, differentiated by treatment arm and by PFS and PPS to arrive at the mean values (95% CI) of Table 18 below.

Table 18. Quality of life values: BEACON EQ-5D averages

	Encorafenib + cetuximab	Control arm
PFS	0.743 (0.732 - 0.753)	0.741 (0.725 - 0.756)
PPS	0.622 (0.581 - 0.662)	0.631 (0.587 - 0.674)

The PFS quality life values are not statistically significantly different by treatment, but the mean values are little different. Similarly, the PPS quality life values are not statistically significantly different by treatment.

4.2.8.2 Quality of life values: Age weighting

The BEACON quality of life values are assumed to apply at baseline. These are age weighted using Ara and Brazier [43] UK population age related average quality of life values.

For instance, at baseline the mean patient age is 59 and the Ara and Brazier population average quality of life is 0.829. After 5 years by age 64 the Ara and Brazier age related quality of life population average has declined to 0.807, or 97% of the age 59 value. Consequently, during year 5 of the model the quality of life values of Table 18 have a 97% weight applied; i.e. the values are 3% less than the values of Table 18.

4.2.8.3 Adverse events and quality of life

No quality of life decrements are applied to adverse events. The company assumes that the BEACON EQ-5D data already incorporates the quality of life effects of adverse events.

4.2.9 Resources and costs

4.2.9.1 Direct drug costs

The company calculated the direct drug costs on a 28-day basis due to the treatment cycles for cetuximab and FOLFIRI being 14 days, and 28 days for trifluridine + tipiracil. The 28-day cost is then increased pro rata to a monthly cost so as to be aligned with the model cycle length.

Oral encorafenib and oral trifluridine + tipiracil are treated similarly.

- The 28-day period requires four 75mg encorafenib tablets daily or 112 tablets in total, equivalent to 2.67 packs of 42 tablets. At a list price of £1,400 this is amounts to £3,733. Increasing this pro rata results in a monthly cost of £4,056.

- The 28-day period requires 10 trifluridine + tipiracil administrations, each requiring six 20mg tablets. Trifluridine + tipiracil is packaged as 60 units so is sufficient for 28 days, with a list price of £2,000. Increasing this pro rata results in a monthly cost of £2,173.

When costing IV chemotherapy, vial sharing between patients is assumed and there is no wastage. The company also applies relative dose intensity (RDI) percentages to account for actual doses received during the trials compared to the planned dosing.

The direct drug costs for the cetuximab loading dose and ongoing administrations are presented in Table 19 below. With a 14-day cycle, 2.17 administrations are required per month. The BEACON cetuximab RDI is also applied, which results in the model applying the costs of the last column.

Table 19. Direct drug costs: cetuximab

	Pack	mg	Cost/mg	Dose	Cost	n/month	£/month	RDI	Applied
Loading	£891	500	£1.78	700	£1,247	1.00	£1,247	87%	£1,084
Ongoing	£891	500	£1.78	900	£1,603	2.17	£3,482	87%	£3,027

For the 1st model cycle the company applies the loading dose cost plus half the ongoing monthly cost, hence a total 1st model cycle cetuximab cost of £2,596. Minor monthly premedication costs for chlorphenamine, hydrocortisone and paracetamol totalling £15 are added to the cetuximab costs. A similar method is applied for the elements of FOLFIRI, resulting in a total monthly drug cost of £89.

Dispensing costs of £15.29 are applied to trifluridine + tipiracil every 28 days, with the monthly model cycle increasing this pro rata to £16.61. The intravenous chemotherapy administration cost is based upon the £233 NHS reference cost for delivering subsequent elements of a chemotherapy cycle. Both cetuximab and FOLFIRI are fortnightly administrations so a 28-day cost of £466, with the monthly model cycle increasing this pro rata to £507. It appears that the dispensing costs for encorafenib are subsumed into the cetuximab IV administration costs.

This results in the following direct drug and administration costs per monthly model cycle.

Table 20. Direct drug and administration costs: monthly model cycle

	ENCO+c	FOLFIRI	T&T
Drug: 1st cycle	£6,667	£89	£2,173
Drug: subsequent cycles	£7,097	£89	£2,173
Administration	£507	£507	£17

4.2.9.2 PPS drug treatment costs

The time spent in PPS does not affect the PPS drug treatment costs.

At progression, patients in the encorafenib + cetuximab arm and in the FOLFIRI arm are assumed to receive an average of one month of treatment with trifluridine + tipiracil at an average cost per patient of £1,936. After this, patients receive no further drug treatment.

4.2.9.3 Health state costs

The ongoing additional monthly resource use, unit costs and total monthly health state costs are presented in Table 21 below.

Table 21. Additional ongoing monthly health state costs

	PFS			
	ENCO+c	FOLFIRI	PPS	Cost
Oral chemotherapy day case	0.50	0.50		£163
Medical oncologist OP visit	0.50	0.50		£227
GP home consultation			0.25	£100
Community nurse specialist visit			1.00	£37
Health home visitor	0.50	0.50	1.00	£46
District nurse visit (PICC line care)		4.00	1.00	£46
GP surgery visit			1.00	£28
Monthly cost	£218	£402	£182	

4.2.9.4 Inpatient costs

Adverse event rates are taken from the BEACON trial for encorafenib + cetuximab andfrom Tabanero et al (2015) for FOLFIRI. Units costs are typically from NHS reference costs, though some adverse events have no cost applied due to company expert opinion. The influential unit costs are for neutropenia, taken from TA439, febrile neutropenia, taken from TA405, livery injury/failure, taken to be the average of NHS reference costs for liver failure codes GC01C, GC01D and GC01E. The adverse event rates, costs and mean cost by treatment arm are presented in Table 22 below.

Table 22. Adverse event rates and costs

	ENCO+c	FOLFIRI	Cost
Abdominal pain		3.6%	£145
Anaemia		3.6%	..
Asthenia		0.0%	£164
Cancer pain		0.0%	£145
Decreased appetite		1.9%	..
Diarrhoea		9.7%	£164
Fatigue		7.8%	£164
Febrile neutropenia		2.5%	£2,807
Hypertension		2.8%	£880
Intestinal obstruction		0.0%	£216
Leukopenia		2.7%	£2,504
Liver injury / failure		4.0%	£2,887
Nausea		2.7%	..
Neutropenia		23.3%	£2,504
Stomatitis		2.3%	£164
Thrombocytopenia		0.8%	£640
Urinary tract infection		0.0%	£216
Venous thrombosis		2.1%	£216
Vomiting		2.5%	£164
Mean total AE cost		£910	

FOLFIRI is estimated to have somewhat higher adverse event costs than encorafenib + cetuximab. This is mainly driven by neutropenia and febrile neutropenia. There is effectively no neutropenia with encorafenib + cetuximab, but around 25% with FOLFIRI.

4.2.9.5 Terminal care costs

One off terminal care costs of £7,162, taken from TA405, are applied for each death. These only slightly affect the net cost effectiveness results of the company base case due to discounting and the small 1.4% proportion of encorafenib + cetuximab patients who are modelled as surviving beyond the 10-year time horizon

4.3 ERG cross check and critique

4.3.1 Base case results

The ERG has rebuilt the company deterministic model using the company preferred assumptions and model inputs and gets complete agreement with the company model build. The ERG model rebuild suggests that within the company model:

- There are some peculiarities in the modelling of the general population OS curves using lifetable data, but that given company assumptions this has little effect upon results.
- In the FOLFIRI arm the monthly £182 PPS cost is applied as the AE cost, rather than the £910 FOLFIRI AE cost estimate.

4.3.2 Data Inputs: Correspondence of written submission with electronic model

The written submission corresponds with the electronic model.

4.3.3 ERG commentary on model structure, assumptions and data inputs

4.3.3.1 Critique of company's modelling of OS and PFS

The company's modelling of OS and PFS for FOLFIRI results in considerable deviations from the observed data in the control arm of BEACON CRC. Figure 17 demonstrates that the modelling of both OS and PFS differ by over 10% (largest underestimate of 16.9 and 12.3 percentage points for OS and PFS, respectively), which contradicts the company's clinical experts who suggested that the additional benefit of cetuximab "could be small" (CS Document B, page 86-87). This reinforces the unsuitability of the indirect comparison, and further motivated the ERG to consider alternative approaches to modelling the OS and PFS curves of FOLFIRI.

Figure 17. Deviation of company modelling of OS and PFS from BEACON CRC trial control arm

4.3.3.2 ERG's exploration of alternative approaches to modelling OS

Given the concerns related to company's ITC described above and in clinical effectiveness Section 3.6, the ERG instead considers fitting parametric curves for both encorafenib + cetuximab and control, using both arms of the BEACON CRC trial. The ERG finds the fit to the encorafenib + cetuximab arm unsatisfactory for any of the statistical models, and because of its abnormal hazard behaviour.

An examination of the models fitted by the company in Figure 5 demonstrates how there is deviation of all curves from the observed data, between months 2 to 4 and months 8 to 10. An examination of the cumulative hazard plot (Figure 18), finds that there is a clear change of trajectory of the hazard rate in this patient population at 2.8 months. Routinely used parametric models do not fit well to data like this, where a hazard rate increases suddenly and then appears to remain constant or decrease slightly over time, and so the ERG sought to fit the models only to data occurring beyond 2.8 months.

Figure 18. Cumulative hazard plot of encorafenib OS data from BEACON CRC trial.

As demonstrated in Figure 19, models fitted to the data beyond 2.8 months cope much better with the hazard behaviour and offer a wide range of potentially plausible models. In this plot, 2.8 months is modelled as time zero, and the proportion of patients alive at 2.8 months in each arm is modelled as 1. Patients who are censored or experienced events before 2.8 months are ignored in the model fitting. It is not assumed that there are equivalent number of patients alive in each arm at 2.8 months, despite appearing this way in the graph. As examined by the company, the assumption of proportional hazards was not violated for the OS data (CS Document B, Figure 8, page 105), and so the ERG

preferred to model both arms simultaneously, in order to maximise the information being used by the models. This was also the basis of the ERG's predictions for the OS of the comparator, rather than rely on the indirect treatment comparison.

Figure 19. Parametric curves fitted to OS data of survival times beyond 2.8 months of trial follow-up from BEACON CRC trial.

The ERG also considered AIC and BIC of the models fitted simultaneously to data from 2.8 months (Table 23). The AIC values are all within a range of 3 units of each other suggesting the models are relatively indistinguishable. Looking at BIC, the exponential model had the lowest though all models were similar, and the ERG were not willing to rule any curves out at this stage, and examined the predictions of the extrapolations.

Table 23. AIC and BIC of models fitted simultaneously to both arms of OS data from BEACON CRC from 2.8 months

Parametric Model	AIC	BIC
Exponential	1481.69	1489.52
Weibull	1481.87	1493.61
Log-normal	1481.93	1493.67
Log-logistic	1478.94	1490.68
Gompertz	1479.00	1490.74
Generalised gamma	1479.08	1494.74

Of the dependent models fitted from 3 months, the log-logistc and Gompertz are probably all too optimistic (Table 24). This leaves exponential, Weibull and generalised gamma. AIC does not allow any distinction between any of the models. As the probability of surviving beyond 5 years seem to be very small for this patient population (see Section 3.5.4), Weibull or exponential would be more suitable than generalised gamma. Looking at the BIC of just these three models, exponential appears to be the best and therefore is chosen for the ERG's base case.

Table 24. OS predictions for both arms of the BEACON CRC trial

Arm/Model	Percentage alive at: (time and the percentage of patients are modelled both from original time = 0)						
	3 years	5 years	10 years		3 years	5 years	10 years
Encorafenib arm				Control arm			
Exponential Weibull Log-normal Log-logistic Gompertz Generalised gamma	[redacted]			Exponential Weibull Log-normal Log-logistic Gompertz Generalised gamma	[redacted]		
Company base case (log-logistic fitted to encorafenib arm)	[redacted]			Company base case (Hazard ratio applied to encorafenib extrapolation)	[redacted]		

4.3.3.3 ERG's exploration of alternative approaches to modelling PFS

The company modelled PFS through fitting curves to the encorafenib + cetuximab arm of the BEACON trial, and extrapolating beyond the observed period of the trial. To estimate PFS for FOLFIRI, the company applied the hazard ratio obtained from the ITC, which used information from the control arm of BEACON CRC and Peeters 2010/2015 trial.[26] This approach utilised the hazard ratio from the ITC performed by the company, which assumed proportionality of hazards within the two trials it included. However, the company themselves state that this assumption is violated, and it led the ERG to prefer modelling with the data from the control arm of the BEACON CRC study.

For the encorafenib + cetuximab arm, the company selected the log-logistic curve based on its AIC and BIC values, having validated its predictions with clinical experts. The ERG accepts the log-logistic as a plausible extrapolation and agreed that it was the best statistical fit according to AIC and BIC. However, the ERG note that it is also the most optimistic of all six extrapolations, providing the

highest estimate of PFS LYs for encorafenib. The log-logistic curve predicts that at least 1% of patients on encorafenib will remain in the PFS health state for up to 3.4 years from the start of the model, which is considerably longer than the present follow-up of the trial. The current maximum observed follow-up time without a PFS event for any patient on encorafenib is less than 23 months, at which point the Kaplan-Meier plot from BEACON estimates 5.3% of patients remain progression-free. In contrast, the company's prediction for FOLFIRI was that less than 1% of patients are predicted to remain in the progression-free health state from 9 months.

The ERG investigated the suitability of fitting parametric curves to the control arm of BEACON CRC, and found all six candidate curves fitted poorly to the observed data (Figure 20). The unusual shape of the survival curve led the ERG to investigate the cumulative hazard plot for the PFS data (Figure 21). The combination of the unusually shaped data, and the maturity of the data led the ERG to prefer to model the PFS data as they were observed in BEACON in the economic analysis, without implementing a parametric curve.

As an alternative scenario, the ERG considered a piecewise approach, selecting a cut point of 1.8 months, beyond which point the hazard behaviour in the control arm is more typical of that which is captured well by the parametric models. The ERG are reluctant to select this approach for their base case analysis as there are less than half of patients remaining at risk of a PFS event at this point in the control arm and the extrapolations may be overly sensitive to outlying events occurring in the tail of the K-M plot. There was no evidence to suggest the assumption of proportionality was violated in the data beyond 1.8 months, and so models were fitted simultaneously to both arms. This also maximised the information being used by the models. Whilst a Cox proportional hazards model did not estimate a significant difference between the arms, the ERG maintained a treatment effect parameter in the model fitting, to allow different hazard rates for both arms of the BEACON CRC trial, because there remained a potential minor benefit of encorafenib + cetuximab. Examination of AIC and BIC suggested that the log-logistic curve was the best fit to the data (Table 25), however the ERG considered the estimates to be too optimistic. The generalised gamma, Gompertz and exponential models were the next best fitting models according to AIC and BIC, and all produced potentially plausible extrapolations. All were considered in scenario analyses.

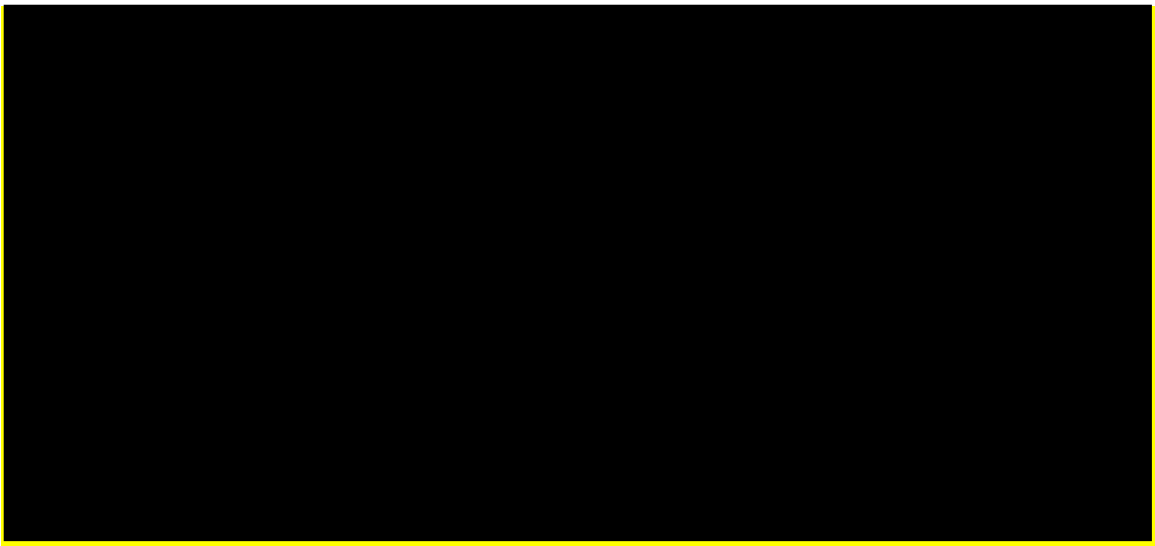

Figure 20. Parametric survival curves fitted to PFS data for control arm of BEACON

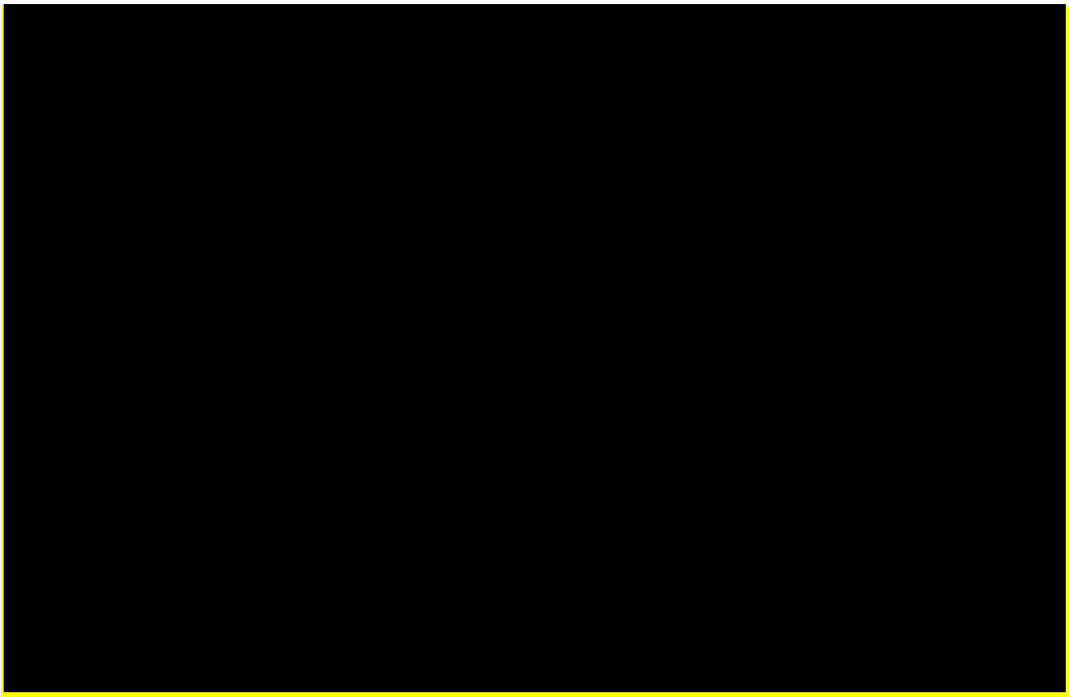

Figure 21. Cumulative hazard of parametric curves fitted to PFS data for control arm of BEACON

Table 25. AIC and BIC for models simultaneously fitted to PFS data from both arms of BEACON from 1.8 months

Parametric Model	AIC	BIC
Exponential	980.838	987.841
Weibull	982.832	993.336
Log-normal	988.588	999.092
Log-logistic	974.592	985.096
Gompertz	980.501	991.005
Generalised gamma	979.306	993.311

4.3.3.4 Choice of parameterised curves: net effects

The BEACON control arm was composed of FOLFIRI + cetuximab (n=129, 58%) and irinotecan + cetuximab (n=92, 48%). The company assumes equivalence between FOLFIRI + cetuximab and irinotecan + cetuximab.

The company ITC estimates OS and PFS hazard ratios for encorafenib + cetuximab compared to FOLFIRI.

Viewed from the perspective of the economic modelling, the ERG thinks that given the availability of the BEACON control arm, the more natural comparison for the ITC is for FOLFIRI + cetuximab vs FOLFIRI; i.e., the ITC could estimate the cetuximab treatment effect among BRAF V600E mutant patients. The resulting treatment effect estimate for cetuximab among BRAF V600E mutant patients might also be more obviously interpretable for reasonableness by the clinical experts. The treatment effect estimate for cetuximab among BRAF V600E mutant patients could then be used in conjunction with the company BEACON control arm parameterised curves to estimate OS and PFS for FOLFIRI.

It would still be possible to apply the original company ITC estimates to the BEACON encorafenib + cetuximab arm parameterised curves as a scenario analysis, or as an analysis of equal importance to that proposed by the ERG. In this regard it should be borne in mind that the company estimates the parameterised curves for each arm of BEACON independently from one another. If the results differed much between the two approaches, the question of which is the more reasonable would require further consideration. It may also be more reasonable to estimate the encorafenib + cetuximab parameterised curves in conjunction with the BEACON control arm parameterised curves, instead of estimating them independently.

The key point is that the currently implicit clinical effectiveness of adding cetuximab to FOLFIRI for the BRAF V600E patient group would be manifest. The relevant HRs used in the ITC are those of

Peeters et al.,[26] of 1.56 for OS and 1.45 for PFS for FOLFIRI relative to FOLFIRI + cetuximab, assuming equivalence between cetuximab and panitumumab. This compares with the HRs of the ITC for FOLFIRI relative to encorafenib + cetuximab of 2.56 for OS and 3.33 for PFS. The ERG will explore both as scenarios.

However as previously reviewed, the ERG thinks that the treatment effect of adding cetuximab to FOLFIRI for the BRAF V600E patient group is relatively minor. The ERG base case models the clinical effectiveness of both arms using the parameterised OS curves for the arms of the BEACON trial and does not apply any hazard ratio for the effectiveness of cetuximab in the control arm of BEACON. Similarly, given the completeness of the BEACON KM PFS curves, the ERG applies the BEACON KM PFS curves for its revised base case. The PFS KM curves show measured progression and have large steps in them at the monthly assessment points. It can be argued that they fit both the BEACON treatment discontinuation data and the BEACON EQ-5D data better than the parameterised PFS curves.

4.3.3.5 Treatment effect duration

The company does not explore possible waning of treatment effect after the trial period, as suggested in the NICE methods guide. The model implementation also makes this problematic. This and time constraint mean that the ERG has also not explored waning the treatment effect.

4.3.3.6 Choice of parameterised curves: net effects

The effect of the choice of functional form for the parameterised curve upon the net survival gain for encorafenib + cetuximab compared to the BEACON control arm is presented in Table 26, with the percentage difference between each functional form and the log-logistic of the company base case being presented in brackets.

Table 26. Net months AUCs: encorafenib + cetuximab vs BEACON control arm

	OS		PFS	
Curve	16 months	10 years	16 months	10 years
Exponential	[redacted]			
Weibull				
Gompertz				
Log-normal				
Gamma				
Log-logistic				

The choice of parameterised curve has little effect upon the modelled net OS at 16 months, but the effect upon the net PFS at 16 months have already become quite apparent. The main effect is upon the OS extrapolation to 10 years.

Turning to the company modelling that applies the various hazard rations as outlined in Section 4.2.7.2 and Section 4.2.7.4 above, for the comparison with FOLFIRI the choice of the parameterised curve upon the net survival gain from encorafenib + cetuximab relative to FOLFIRI is presented in Table 27.

Table 27. Net months AUCs: encorafenib + cetuximab vs FOLFIRI modelled using ITC HRs

	OS		PFS	
Curve	16 months	10 years	16 months	10 years
Exponential	[redacted]			
Weibull				
Gompertz				
Log-normal				
Gamma				
Log-logistic				

The picture is much the same for the company base case comparison of encorafenib + cetuximab with FOLFIRI, which applies the 2.56 OS HR and 3.33 PFS HR to the encorafenib + cetuximab curves to derive the FOLRFIRI curves. The Weibull estimates [redacted] less net OS gain at 10 years and [redacted] less net PFS gain compared to the company base case log-logistic estimates. The above also illustrates the large difference in net OS gain between the BEACON arms, [redacted] months, and encorafenib + cetuximab and FOLFIRI, 10.1 months, based upon the log-logistic.

In summary, the AIC and BIC of the fitted curves relates to the goodness of fit during the trial period. They may be a poor guide as to the reasonableness of extrapolating the curves to 10 years. The choice of functional form has some effect upon the net OS gains and net PFS gains that are modelled to 16 months but this is relatively muted. The choice of curve has a much larger effect upon the net OS gains and net PFS gains extrapolated to 10 years.

4.3.3.7 Post progression survival gains

The company model anticipates that encorafenib + cetuximab will result in overall survival gains, and that the majority of these gains occurs after progression when treatment with encorafenib + cetuximab is assumed to have ceased.

The CR response to A4 provides the BEACON Kaplan Meier data for PPS, with the date of the first assessment of patients having progressed being treated as the baseline Day = 0. Figure 22 presents the BEACON PPS KM data for the encorafenib + cetuximab arm, the control arm and the FOLFIRI + cetuximab subset of the control arm. The patients remaining at risk are presented as proportions of the PPS Day = 0 number of patients, [redacted].
The numbers at risk for the FOLFIRI + cetuximab subset of the control arm are not presented to avoid confusing an already busy graph.

Figure 22. BEACON PPS KM curves

Figure 22 comes with health warnings. The Day = 0 number of patients in the encorafenib + cetuximab arm is larger than in the control arm, despite balance between the two at trial baseline. This seems likely to be due to fewer encorafenib + cetuximab progressions being deaths. The encorafenib + cetuximab PPS KM data also has considerably more censoring, [redacted], than the control arm PPS KM data, [redacted], with virtually all of this censoring being due to the data cut-off date. This may mean that randomisation is breaking down in the PPS Kaplan Meier data, and the timing of events is obviously no longer aligned.

There appears to be no difference in PPS during the first three months after progression. Any apparent superiority in the encorafenib + cetuximab arm only emerges after three months post progression. There may be some suggestion that the PPS of the FOLFIRI + cetuximab patients of the control arm, [redacted], may be superior to the PPS of the irinotecan + cetuximab patients of the control arm[redacted] but this is not particularly marked.

The source of the possible difference in PPS is unclear. There may be some ongoing effect from treatment that endures after progression and patients have ceased treatment, or patients may continue with treatment after progression, or it could be some combination of the two. But the ERG finds it difficult to rationalise why either of these reasons would cause there to be no difference in PPS during the first three months post progression, but for a difference to emerge thereafter.

The numbers at risk also begin to separate from the PPS KM curves from three months. For both encorafenib + cetuximab and the control arm, around [redacted] of patients remain at risk at around 10 months PPS. At this point the areas under the KM curves are [redacted] months for encorafenib + cetuximab, [redacted] months for the control and [redacted] months for the FOLFIRI + cetuximab patients of the control arm: net gains from encorafenib + cetuximab compared to the control arm of [redacted] and compared to the FOLFIRI + cetuximab patients of the control arm of [redacted]

The above relates to those who survive measured progression and proceed to post progression survival. If more survive measured progression in the encorafenib + cetuximab arm than in the control arm, or than in the control arm FOLFIRI + cetuximab subset, the average PPS survival would be higher in the encorafenib arm than in the control arm.

The area under the PPS KM S(t) curves between measured progression and 15 months subsequent to measured progression is around [redacted]months, and perhaps a little higher in the encorafenib + cetuximab arm at [redacted] months compared to [redacted] months in the control arm, and [redacted] months in the control arm FOLFIRI + cetuximab subset. As already noted, the PPS numbers at risk at Day = 0 in the encorafenib + cetuximab arm is around [redacted] greater than that in the control arm. This is higher than the proportion

of PFS events that are reported as progressions rather than deaths: [redacted] in the encorafenib + cetuximab arm compared to [redacted] in the control arm. But even retaining the [redacted] of the PPS KM data taken together with the PPS AUCs to month 15 only suggests a mean PPS gain of [redacted] months among encorafenib + cetuximab patients compared to FOLFIRI + cetuximab patients.

4.3.3.8 Treatment effectiveness: TTD and PFS curves: BEACON encorafenib + cetuximab

The ERG presented the BEACON PFS and TTD KM plots in Section 4.2.7.5 above. The ERG thinks that the company is incorrect to conclude that because the TTD KM curve is not statistically different from the PFS KM curve, it should be assumed that the TTD curve is the same as the PFS curve. It seems unlikely that the company would argue the converse: that the PFS curve should be assumed to be the same as the TTD curve.

The ERG thinks that given the trial protocol it should not be expected that BEACON would demonstrate statistical difference between TTD and PFS even if such a difference exists. The ERG notes that for encorafenib + cetuximab the proportion remaining on treatment in the TTD curve in Figure 15 is greater than the proportion remaining progression free from month 5.

The treatment of some events also differs between the TTD curve and the PFS curve. For instance, withdrawal of consent and receipt of subsequent treatment are both treated as discontinuation events in the TTD curve but as censoring events in the PFS curve. The ERG does not have sufficient access to the IPD and data definitions to know if there are other events which may be treated as discontinuation events in the TTD curve but as censoring events in the PFS curve. Intuitively, since the license for encorafenib + cetuximab specifies use throughout PFS it might be expected that treatment discontinuation events should be treated as informative censoring rather than as uninformative censoring. This is not easily achieved within the KM data, the only readily available alternative being to treat these events in a like manner in the TTD curve; i.e. as uninformative censoring rather than as events. This causes the TTD curve to rise slightly as shown in Figure 23 below, but the effect is not dramatic.

Figure 23. BEACON PFS and TTD KM curves: Encorafenib + cetuximab: censoring effects

In the light of the TTD and PFS curves the ERG thinks that for encorafenib + cetuximab the proportion remaining on treatment during BEACON was greater than the proportion remaining progression free.

4.3.3.9 Treatment effectiveness: TTD and PFS curves: BEACON control arm

The picture is more mixed for the BEACON control arm, with Figure 16 perhaps suggesting that the TTD curve typically lies on or only just below the PFS curve for the first two months, but thereafter lies below it. This is complicated by the control arm being composed of FOLFIRI + cetuximab and irinotecan + cetuximab. The CR data for Issue 4 does not particularly suggest that the FOLFIRI + cetuximab patients' (n=129/221) TTD and PFS KM curves are more closely aligned than those of the irinotecan + cetuximab patients (n=92/221), only the former being presented as Figure 24 for reasons of space.

Figure 24. BEACON PFS and TTD KM curves: FOLFIRI + cetuximab

The ERG thinks that the alignment between the TTD and PFS KM curves of the BEACON FOLFIRI + cetuximab patients of Figure 24 above suggests that the TTD curve tends to lie below the PFS curve by slightly more than for the BEACON control arm as presented in Figure 16 on page 75 above.

4.3.3.10 Quality of life during PFS: BEACON EQ-5D data

The company analysis of the BEACON PFS EQ-5D data is limited to taking the means of the reported EQ-5D values, differentiated by arm: 0.743 for the encorafenib + cetuximab arm and 0.741 for the control arm.

The first point to note is that the mean value at screening was slightly lower in the encorafenib + cetuximab arm, compared to the control arm, . This could in itself account for the difference between the arms' PFS quality of life values in the company base case.
This analysis also does not take into account the possible effects of the PFS patient mix changing over time, or individual patient's quality of life changing over time while remaining in PFS. It is conceivable that patients with a poor baseline quality of life had a worse prognosis and tended to progress more quickly. If patients' quality of life during PFS remained constant, the mean quality of life of those remaining in PFS would tend to rise over time.

The mean PFS quality of life, upper and lower confidence intervals[2] and contributing number of observations by BEACON cycle[3], as per CR question B3 Issue 2[4], are presented in Figure 25 and Figure 26 below.

Figure 25. BEACON PFS EQ-5D: Encorafenib + cetuximab

[2] Based upon 1.96*s.e.
[3] Some observations were not on day 1 of the relevant cycle. A small number of observations, 12, typically reported on day 22 of the previous cycle were attributed to 1st day of the subsequent cycle due to this being the nearer timepoint.
[4] The ERG has also reviewed the subgroup data supplied for 1 prior vs 2 prior and for the control arm split by FOLFIRI + cetuximab and irinotecan + cetuximab, but views this section which concentrates upon each arm's pooled data as sufficient.

Figure 26. BEACON PFS EQ-5D: Control arm

The first point to note is that in the CR the mean PFS quality of life values weighted by the number of observations are [redacted] for the encorafenib + cetuximab arm and [redacted] for the control arm, whereas the company model applies [redacted] for encorafenib + cetuximab and [redacted] for FOLFIRI.

For the encorafenib + cetuximab arm the mean quality of life appears to be reasonably constant. There may be a suggestion of a slight increase after around month 15, but this is based upon small numbers of observations.

As would be expected, the number of PFS observations drops considerably more quickly in the control arm than in the encorafenib + cetuximab arm. Up to cycle 10 the mean quality of life holds reasonably steady. There may be some suggestion of a slight decline thereafter, but this is based upon very small numbers of observations.

The ERG thinks that given the above and in the absence of other information it is reasonable to assume that the average quality of life among those remaining progression free remains reasonably constant over time. Whether this is due to individual patient's PFS quality of life holding steady or individual patient's PFS quality of life declining but the PFS patient population mix changing over time with the less healthy progressing cannot be stated. Something along the lines of a repeated measures analysis with a time coefficient would be required to answer this. If a negative time coefficient were uncovered, the PFS quality of life value applied to the extrapolated PFS curves would be too high and could bias the analysis in favour of encorafenib + cetuximab.

There is also the concern that if progression affects the patient mix and the resulting mean quality of life value, because progression is more rapid in the control arm then this may be a contributory factor to its mean BEACON PFS quality of life being slightly lower than that of the encorafenib + cetuximab arm.

4.3.3.11 Quality of life during PPS: BEACON EQ-5D data

For PPS, the company applies the BEACON mean post progression EQ-5D values, differentiated by arm. The CR question B3 Issue 2 reports the PPS quality of life data, mean, 95% CI and N observations, also splitting the control arm by treatment as per below.

Table 28. BEACON PPS EQ-5D data: encorafenib + cetuximab

	EQ-5D	N
End of treatment	[redacted]	
30 Day follow-up		
Weighted mean		

Table 29. BEACON PPS EQ-5D data: control arm

	CTRL		FOLFIRI + c		IRIN + c	
	EQ-5D	N	EQ-5D	N	EQ-5D	N
End of treatment	[redacted]					
30 Day follow-up						
Weighted mean						

The first point to note is that the PPS EQ-5D data only extends to 30 days post progression follow-up. The mean PPS duration for encorafenib + cetuximab in the company base case is 9.4 months. It seems possible that quality of life in PPS will decline over time.

The second point to note is that the PPS quality of life values for FOLFIRI + cetuximab are somewhat better than those for irinotecan + cetuximab. The ERG does not have the 95% CIs for the weighted mean and cannot concluded whether they are statistically significantly different, but both encorafenib + cetuximab and FOLFIRI + cetuximab are somewhat above the corresponding irinotecan + cetuximab values. Furthermore, the FOLFIRI + cetuximab value is somewhat above the encorafenib + cetuximab value. This may be due to the changing mix of patients in the PPS health state and the timing of their progression.

For the comparison of encorafenib + cetuximab with FOLFIRI the ERG revised base case will apply the treatment specific values.

4.3.3.12 Quality of life: TA405

The company submission for TA405 averaged EQ-5D quality of life values across those of the trifluridine + tipiracil CORRECT study and those of the cetuximab submission for 1st line mCRC treatment. The ERG preferred to use just the CORRECT trial values, and the AC noted that averaging was methodologically unsound. The CORRECT trial values were 0.74 to 0.74 for PFS and 0.59 for PPS. In the light of trifluridine + tipiracil typically being a later line of treatment, this may suggest that patient quality of life among those fit for treatment holds up reasonably well, but that there may be some reduction in quality of life after progression and when treatment options begin to run out.

4.3.3.13 Direct drug costs: Encorafenib + cetuximab

The 1st cycle cost of cetuximab differs from subsequent cycles due to a loading dose. The ERG thinks that the SmPC specifies this as a 7 day loading dose, after which ongoing cetuximab dosing is applied. The company costs the 1st cycle as the loading dose plus half the ongoing monthly cost.
ERG expert opinion is split about this, suggesting practice may vary. One expert is aligned with the above. The other suggests that with fortnightly dosing there is no need for the lower dose loading and that patients can receive the full maintenance dose on a fortnightly basis from the start of treatment. Since the company model applies the lower loading dose, the ERG revises the next dose to be received on day 8. For the first model cycle, the ERG applies the loading dose plus three quarters of the ongoing monthly cost and will apply this in its revised base case.

4.3.3.14 Direct drug costs: FOLFIRI

The company applies a simple unweighted average to arrive at an average cost of £24.45 for each 700mg dose of folinic acid, when conditioned by the [redacted] RDI. But this would be available more cheaply using 350mg vials at costs of [redacted] when it is conditioned by the [redacted] RDI, and [redacted] when it is not. The ERG will apply these prices.

The company applies a simple unweighted average to arrive at an average cost of £39.59 for each 5g dose of fluorouracil, when conditioned by the [redacted] RDI. This simple average cost includes £134 based upon using packs of 250mg, available in packs of 5 for £23.76, and also includes £96.49 based upon using packs of 500mg, available in packs of 10 for £66.00. Within the CMU EMIT database[5],

[5] Accessed 4 April 2020.

the 250mg*5 does not seem to be listed. The CMU EMIT database suggests that of the formulations available only 0.6% are based upon using packs of 500mg in packs of 10 for £66.00, and that the somewhat cheaper single 500mg packs at £0.98 are more often used, with 8% of the CMU EMIT volume. But by far the most frequently used are the 1g and 2.5 g packs, with an average 5g cost of between £6.64 to £8.26. In the light of this, the ERG applies a CMU EMIT weighted average cost of [redacted] per 5g fluorouracil dose when the RDI of [redacted] is applied and [redacted] when it is not.

The company applies a simple unweighted average to arrive at an average cost of [redacted] for each 320mg dose of irinotecan, when conditioned by the [redacted] RDI. The differences with the CMU EMIT database are inconsequential.

4.3.3.15 Direct drug costs: Trifluridine + tipiracil

Trifluridine + tipiracil is available as a combination tablet as Lonsurf. The SmPC suggests a daily dose of six 20mg/8.19mg combination tablets on 10 days per 28 day cycle. The BNF gives a list price of £2,000 per 60 tablet pack; i.e. per 28 days. The 17 Feb 2020 CS infers and applies a PAS inclusive price for Lonsurf, based upon TA405. All results in this document apply the list price of Lonsurf. The PAS inclusive results are presented in the cPAS appendix.

4.3.3.16 Relative dose intensities

For the IV administrations the company applies relative dose intensity percentages. This mainly reduces the cetuximab costs in the encorafenib + cetuximab arm, and the ERG concentrates upon this in what follows. Within the BEACON encorafenib + cetuximab arm the company reports the cetuximab RDI data of Table 30.

Table 30. BEACON cetuximab RDI and treatment exposure data

	Weeks	RDI
Less than 50%	[redacted]	
50% to 80%		
80% to 100%		
More than 100%		
Min		
Max		
Median		
Mean		

The RDI data is quite skewed. A few patients have a very poor experience, while the majority fare somewhat better. The data used to calculate the RDI and how it has been combined is unclear, and the ERG did not ask about this at clarification. But the median RDI is somewhat higher than the mean RDI, and the RDI is applied over the entire model time horizon. The ERG thinks it likely that the skewness of RDI is due to some patients faring poorly in the early period of the trial, with those remaining within the trial and in PFS for longer, having a better RDI. As a consequence, applying the mean RDI during the period of the trial will tend to underestimate actual cetuximab use. And extrapolating using the mean is likely to lead to further bias.

The cetuximab SmPC notes that infusion reactions may cause less than the prepared dose to be administered, but this would still incur the drug cost of the prepared dose. The cetuximab SmPC also notes that if there is a treatment holiday due to adverse reactions, treatment with cetuximab may recommence at the same dose, but that treatment after subsequent treatment holidays may begin at reduced doses, 80% and 60%, after which if adverse events continue cetuximab should be discontinued.

Given the above, the BEACON adverse event frequencies and the company base case RDIs, the ERG thinks that if an RDI is to be applied it should only relate to treatment reductions and/or treatment holidays, unless there is good evidence to the contrary. The company has not presented explicit evidence on dose reductions and/or treatment holidays and their timing within BEACON.

It can be noted that the draft SmPC states that if encorafenib is discontinued cetuximab should be discontinued but that encorafenib may be continued if cetuximab is discontinued. The calculation of the RDI and its application should also be considered alongside the TTD curves of Section 4.3.3.8. It may be that the TTD curves capture some or all of the RDI considerations, and the application of the RDI may involve a degree of double counting.

In the light of the above the ERG will apply the median RDIs in its revised base case, and present scenario analyses of RDIs of 100% and RDIs of the company base case.

4.3.3.17 BRAF V600E testing costs

The scope specifies that: “The use of encorafenib in dual or triple therapy is conditional on the presence of BRAF V600E mutation. The economic modelling should include the costs associated with diagnostic testing for BRAF V600E mutation 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.”

The company does not include any BRAF V600E testing costs on the grounds that mCRC patients will be tested for BRAF V600E mutation status and the introduction of encorafenib will not affect this. As noted by the ERG in the clinical review, NG151 recommends testing all mCRC patients suitable for systemic anti-cancer treatment for BRAF V600E mutations due to the mutation predicting EGFR response.

In the light of this the ERG thinks it is reasonable that cost of BRAF V600E testing should not be included.

4.3.3.18 Vial sharing

For the IV administrations the company assumes that vials can be shared between patients and that there is no waste. This mainly reduces the cetuximab costs in the encorafenib + cetuximab arm. ERG expert opinion suggests that vials are shared between patients when possible, but that there is still wastage due to this being less than perfect. It is also complicated to achieve in smaller clinics. The ERG will assume there is vial sharing in its revised base case, but will explore the no vial sharing in a scenario analysis

4.3.3.19 Half cycle correction: Minor Issue

The company model applies half cycle correction.

Within a model with a monthly cycle length this typically has little effect upon net patient outcomes, though the poor prognosis and limited survival for the patient group under consideration may mean this is more of a concern.

The main effect of half cycle correction is often to lessen the direct drug costs, and in particular to lessen the typically quite substantial direct drug costs of the intervention. The current model is unusual in that the 1st model cycle differs from all subsequent model cycles. For the 1st model cycle it is assumed that 100% of the baseline population are eligible for treatment, albeit conditioned by the RDIs. For all subsequent model cycles half cycle correction is applied, but e.g. the 2nd cycle is based upon averaging the baseline and end of 1st cycle proportions to determine the half cycle corrected proportion.

The ERG thinks that, given the model cycle length, the most appropriate method is to condition the direct drug costs by the proportion remaining eligible for treatment at the start of the cycle but to calculate the patient benefits and QALYs based upon a half cycle correction.

Given the treatment of the drug costs during the 1st model cycle it is unclear quite how this would affect results, but the company model does not appear obviously biased in this regard. Work using the ERG model rebuild suggests that any effects are minor.

4.3.3.20 Administration, monitoring and other costs during PFS

ERG expert opinion suggests monthly OP visits in addition to administration costs during PFS. Since chemotherapy administration is costed separately, the ERG revises the monthly number of additional administration visits from 0.5 to 0.0, and increases the number of OP visits from 0.5 to 1.0.
ERG expert opinion notes that PICC resource use appears high, and that Portacath use would tend to reduce it further. As a consequence, the ERG reduces the number of monthly district nurse visits for FOLFIRI treatment to 2.

4.3.3.21 Administration, monitoring and other costs during PPS

ERG expert opinion thinks that 50% of patients receiving subsequent treatment is probably about right. But among those receiving PPS treatment, it may be 2-4 months. The ERG notes the modelled PPS survival gains from encorafenib + cetuximab which may suggest greater PPS treatment in the encorafenib + cetuximab arm than the FOLFIRI arm. The ERG presents a scenario analysis where the PPS treatment costs in the encorafenib + cetuximab arm are increased proportionately to the PPS survival gain relative to that modelled for the FOLFIRI arm.

ERG expert opinion suggests that the company estimates of community resource use during PPS may be higher than usual, at least until terminal care, which the company costs separately. But there may be ongoing hospital visits, in part due to this being what patients are used to.

4.3.3.22 Adverse event rates

The BEACON grade 3+ adverse event rates for encorafenib + cetuximab, FOLFIRI + cetuximab and irinotecan + cetuximab are presented in Table 31 below, alongside the estimates taken from the company. This relies upon the CR A13 data, within which there is no read across for the encorafenib + cetuximab to CS Table 16. The CR A13 data appears to be correct for FOLFIRI + cetuximab and for irinotecan + cetuximab, but the ERG has had to make some assumptions in terms of the read across between events in CR A13 and in CS Table 16:

- Cancer pain not reported due to <2% in all arms in BEACON, so taken to be 0%.
- Small intestinal obstruction + intestinal obstruction ≡ intestinal obstruction
- White blood cell count decreased ≡ leukopenia
- Liver injury / failure not reported due to <2% in all arms in BEACON, so taken to be 0%.

- Thrombocytopenia and UTI not obviously reported, so taken to be 0%.
- Pulmonary embolism ≡ venous thrombosis

Table 31. BEACON grade 3+ adverse event rates and costs

	BEACON grade 3+ AEs				
	ENCO+c	FOLF+c	IRIN+c	FOLFIRI	Cost
Abdominal pain	[redacted]			3.6%	£145
Anaemia				3.6%	..
Asthenia				0.0%	£164
Cancer pain				0.0%	£145
Decreased appetite				1.9%	..
Diarrhoea				9.7%	£164
Fatigue				7.8%	£164
Febrile neutropenia				2.5%	£2,807
Hypertension				2.8%	£880
Intestinal obstruction				0.0%	£216
Leukopenia				2.7%	£2,504
Liver injury / failure				4.0%	£2,887
Nausea				2.7%	..
Neutropenia				23.3%	£2,504
Stomatitis				2.3%	£164
Thrombocytopenia				0.8%	£640
UTI				0.0%	£216
Venous thrombosis				2.1%	£216
Vomiting				2.5%	£164
Mean total AE cost	xxx			£910	

Given the lack of BEACON data for FOLFIRI + cetuximab and irinotecan + cetuximab for cancer pain, thrombocytopenia and UTI, when calculating the mean BEACON grade 3+ adverse event costs the ERG also sets these to 0% for encorafenib + cetuximab.

Unless cetuximab is protective against grade 3+ AEs and in particular against neutropenia, the ERG thinks it is more consistent to apply the BEACON FOLFIRI + cetuximab mean grade 3+ AE cost of [redacted] than the company base case estimate of £910.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The deterministic cost effectiveness results are presented for the pairwise comparisons and fully incrementally below. Given the naïve comparison with trifluridine + tipiracil the ERG thinks that it is sensible to retain the pairwise comparisons.

The following results apply list prices for all treatments. The confidential cPAS appendix presents the corresponding analyses that include encorafenib and comparators confidential patient access scheme (PAS) price reductions on their list prices.

Table 32. Company deterministic base case: cost estimates

				ENCO+c net vs comp.	
	FOLFIRI	T&T	ENCO+c	FOLFIRI	T&T
Treatment costs	£316	£5,119	£54,036	£53,720	£48,918
Administration cost	£1,806	£39	£3,889	£2,083	£3,850
AE cost	£182	£1,646	£78	-£104	-£1,568
Subsequent treatment	£1,002	£0	£795	-£206	£795
Health state costs	£2,067	£908	£3,255	£1,188	£2,347
Terminal care cost	£7,018	£7,070	£6,755	-£263	-£315
Total	£12,391	£14,782	£68,809	£56,418	£41,637

Table 33 reports the undiscounted months survival by health state, and the pairwise net loss for the comparators relative to encorafenib + cetuximab.

Table 33. Company deterministic base case: undiscounted months survival

				ENCO+c net vs comparator		
	PFS	PPS	Total	PFS	PPS	Total
FOLFIRI	3.6	3.6	7.1	4.3	5.9	10.1
Trifluridine + tipiracil	2.4	2.2	4.5	5.5	7.2	12.7
Encorafenib + cetuximab	7.9	9.4	17.3	..	..	..

The model estimates that the majority of the survival gain from encorafenib + cetuximab occurs after progression.

Table 34 reports the discounted QALYs by health state, and the pairwise net loss for the comparators relative to encorafenib + cetuximab.

Table 34. Company deterministic base case: discounted QALYs

				ENCO+c net vs comparator		
	PFS	PPS	Total	PFS	PPS	Total
FOLFIRI	0.220	0.182	0.402	0.253	0.262	0.516
Trifluridine + tipiracil	0.145	0.113	0.258	0.328	0.332	0.659
Encorafenib + cetuximab	0.473	0.444	0.917	..	..	..

Due to the quality of life value for PFS being higher than the quality of life value for PPS, while the majority of the QALY gains from encorafenib + cetuximab occurs after progression, the difference between the PFS QALY gains and the PPS QALY gains are less marked than the corresponding survival differences.

Three comparators could argue for a fully incremental analysis, but the naïve comparison with trifluridine + tipiracil argues for separate consideration of the pairwise cost effectiveness of encorafenib + cetuximab versus FOLFIRI and of encorafenib + cetuximab versus trifluridine + tipiracil. Table 35 presents the pairwise cost effectiveness estimates.

Table 35. Company deterministic base case: pairwise incremental costs, QALYs and ICERs

			ENCO+c net vs comparator		
	Costs	QALY	Δ Costs	Δ QALYs	ICER
FOLFIRI	£12,391	0.402	£56,418	0.516	£109k
Trifluridine + tipiracil	£14,782	0.258	£54,027	0.659	£81,949
Encorafenib + cetuximab	£68,809	0.917			

Because there are only three comparators, the fully incremental analysis is easily seen in Table 35. Trifluridine + tipiracil is more costly but less effective than FOLFIRI so is dominated by it. This leaves only the comparison of encorafenib + cetuximab versus FOLFIRI and the cost effectiveness estimate of £109k per QALY at list prices.

Table 36 presents the probabilistic model central estimates running the model over 10,000 iterations.

Table 36. Company probabilistic base case: pairwise incremental costs, QALYs and ICERs

			ENCO+c net vs comparator		
	Costs	QALY	Δ Costs	Δ QALYs	ICER
FOLFIRI	£12,405	0.426	£56,526	0.495	£114k
Trifluridine + tipiracil	£14,152	0.260	£54,778	0.662	£82,761
Encorafenib + cetuximab	£68,931	0.922			

The probabilistic model estimates similar central costs as the deterministic model. But the net QALY gain estimates for encorafenib + cetuximab relative to FOLFIRI are a bit smaller, causing a corresponding worsening of the ICER.

The probabilistic model estimates that there is 0% probability of encorafenib + cetuximab being cost effective at all willingness to pay thresholds up to £50k per QALY.

5.2 Company sensitivity analyses

The data underlying the CS tornado diagrams, revised to be at list prices are presented in Table 37 and Table 38 below.

Table 37. Company DSA: 10 most influential inputs: ENCO + c vs FOLFIRI

	Low value	High value
E+C PFS utility (0.67 to 0.82; base case 0.74)	£121k	£100k
E+C PPS utility (0.56 to 0.68; base case 0.62)	£120k	£101k
Encorafenib list price (£1,260.00 to £1,540.00; base case £1,400.00)	£103k	£116k
OS hazard ratio for mortality; FOLFIRI (2.31 to 2.82; base case 2.56)	£116k	£105k
FOLFIRI PFS utility (0.67 to 0.81; base case 0.74)	£105k	£114k
Cetuximab RDI (maintenance) ([redacted])	£105k	£114k
Cetuximab list price (maintenance) (£801.45 to £979.55; base case £890.50)	£105k	£114k
FOLFIRI PPS utility ([redacted])	£106k	£113k
Mean BSA (1.61 to 1.97; base case 1.79)	£105k	£110k
Vial administration costs (£209.91 to £256.55; base case £233.23)	£109k	£110k

Table 38. Company DSA: 10 most influential inputs: ENCO + c vs T&T

	Low value	High value
E+C PFS utility (0.67 to 0.82; base case 0.74)	£87,247	£77,258
E+C PPS utility (0.56 to 0.68; base case 0.62)	£87,078	£77,391
Encorafenib list price (£1,260.00 to £1,540.00; base case £1,400.00)	£77,228	£86,670
Cetuximab RDI (maintenance) ([redacted])	£78,655	£85,243
Cetuximab list price (maintenance) (£801.45 to £979.55; base case £890.50)	£78,655	£85,243
Mean BSA (1.61 to 1.97; base case 1.79)	£78,055	£81,226
OS HR for mortality; trifluridine/tipiracil (3.60 to 4.40; base case 4.00)	£83,431	£80,755
T&T PFS utility (0.67 to 0.81; base case 0.74)	£81,056	£82,862
T&T PPS utility (0.57 to 0.69; base case 0.63)	£81,250	£82,661
Vial administration costs (£209.91 to £256.55; base case £233.23)	£81,359	£82,539

Common elements to both analyses are the quality of life values, the cetuximab RDI and the OS hazard ratios. The cetuximab price and amount required, proportionate to patients' BSA, also affect results.

5.3 Company scenario analyses

The CS presents a number of scenario analyses, summarised in Table 39 below.

Table 39. Company scenario analyses

	ICER for ENCO + c	
	vs FOLFIRI	vs T&T
Weibull curves rather than log-logistic	£142k	£96,098
Using BEACON control arm as comparator	£199k	..
Assuming T&T as effective as company base case FOLFIRI ITC	..	£98,786
BRAF v600 HRs vs BRAF wild type: 2.24 rather than OS 4.00 & PFS 3.57	..	£92,534
T&T trial utilities: PFS 0.720 and PPS 0.590	..	£80,642
5 year time horizon	£120k	£88,038

5.4 Company piecewise curves

The electronic copy of the company model contains ICERs for piecewise curves compared to the continuous parameterised curves presented in the CS. The ERG has not managed to replicate any of these analyses. It also seems likely that these are based upon the PAS discounted encorafenib price, the [redacted] Lonsurf price and list price for other treatments, as per the analyses of the 17 Feb 2020 CS. The reported ICERs of the piecewise curves are somewhat worse than those of the continuous parameterised curves. Table 40 reports the ICERs for the piecewise curves as a proportion of the corresponding ICERs for the continuous parameterised curves presented in the CS, when the same functional form for PFS and OS are assumed.

Table 40. Company piecewise curves' ICERs relative to continuous parameterised curves' ICERs

	Expo.	Weib.	Gompertz	Log-Norm	Gamma	Log-Log
Exponential	108%	118%	130%	111%	Dominated	117%
Weibull	109%	120%	134%	112%	Dominated	118%
Gompertz	108%	117%	126%	111%	Dominated	116%
Log-Normal	113%	124%	138%	115%	Dominated	121%
Gamma	106%	115%	122%	109%	Dominated	114%
Log-Logistic	118%	130%	146%	120%	Dominated	126%

The ERG has not managed to source the parameter estimates or the information criteria for the piecewise curves and did not ask about this at clarification. A free text search for "piece" of the CS Document A, Document B and Document B Appendices yields no matches.

The ERG is concerned that the company may have undertaken additional analyses that it has not presented but that may be valid and preferable on grounds of clinical reasonableness, visual inspection, or information criteria.

The company base case assumes log-logistic for both PFS and OS, which if the most appropriate combination for the piecewise curves with the piecewise curves being preferable causes the ICER to worsen by 26%.

The ERG thinks that during technical engagement the company should present the basis of the piecewise curves, the curves and the reason(s) for their rejection, together with an electronic model copy that implements these curves.

5.5 Model validation and face validity check

The company states that model validation was undertaken by two health economists, this consisting of internal model cross checking and cross checking the derivation of the input parameters. The company does not provide any validation of the model outputs by comparing them with values within the literature.

Table 41. Company OS estimates: Encorafenib + cetuximab + BEACON KM

Month	EXPO	WEIB	GOMP	LOGN	GAMM	LOGL	KM
12	44%	43%	44%	43%	42%	41%	42%
24	20%	13%	15%	20%	17%	18%	20%
36	8.7%	3.1%	3.1%	11%	7.3%	9.8%	
60	1.7%	0.1%	0.0%	4.6%	1.7%	4.4%	
120	0.0%	0.0%	0.0%	1.0%	0.1%	1.4%	

Table 42. ERG OS estimates: Encorafenib + cetuximab

Month	EXPO	WEIB	GOMP	LOGN	GAMM	LOGL
12	42%	42%	41%	40%	41%	40%
24	15%	16%	20%	22%	19%	20%
36	5.2%	6.7%	13%	14%	10%	13%
60	0.6%	1.2%	7.8%	7.6%	3.8%	7.4%
120	0.0%	0.0%	5.8%	2.9%	0.6%	3.3%

Table 43. Company OS estimates: FOLFIRI with HR applied + BEACON KM

Month	EXPO	WEIB	GOMP	LOGN	GAMM	LOGL	KM
12	12%	12%	12%	11%	11%	10%	25%
24	1.5%	0.5%	0.7%	1.7%	1.0%	1.2%	
36	0.2%	0.0%	0.0%	0.4%	0.1%	0.3%	
60	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
120	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	

Table 44. ERG OS estimates: FOLFIRI

Month	EXPO	WEIB	GOMP	LOGN	GAMM	LOGL
12	25%	25%	25%	27%	26%	26%
24	5.2%	6.4%	8.7%	13%	9.4%	12%
36	1.1%	1.7%	4.5%	8.0%	4.3%	7.4%
60	0.0%	0.1%	2.2%	4.0%	1.2%	4.1%
120	0.0%	0.0%	1.4%	1.3%	0.1%	1.8%

Table 45. Company PFS estimates: Encorafenib + cetuximab + BEACON KM

Month	EXPO	WEIB	GOMP	LOGN	GAMM	LOGL	KM
12	16%	10%	13%	13%	12%	12%	9.2%
24	2.5%	0.2%	0.3%	2.6%	1.5%	3.1%	
36	0.4%	0.0%	0.0%	0.8%	0.3%	1.4%	
60	0.0%	0.0%	0.0%	0.1%	0.0%	0.5%	
120	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	

Table 46. ERG PFS estimates: Encorafenib + cetuximab

Month	EXPO	WEIB	GOMP	LOGN	GAMM	LOGL
12	12%	12%	14%	17%	14%	15%
24	1.2%	1.3%	3.1%	6.1%	2.7%	5.6%
36	0.1%	0.1%	1.2%	3.1%	0.7%	3.1%
60	0.0%	0.0%	0.4%	1.2%	0.1%	1.5%
120	0.0%	0.0%	0.2%	0.2%	0.0%	0.6%

Table 47. Company PFS estimates: FOLFIRI with HR applied + BEACON KM

Month	EXPO	WEIB	GOMP	LOGN	GAMM	LOGL	KM
12	0.2%	0.0%	0.1%	0.1%	0.1%	0.1%	6.2%
24	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
36	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
60	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
120	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	

Table 48. ERG PFS estimates: FOLFIRI

Month	EXPO	WEIB	GOMP	LOGN	GAMM	LOGL
12	4.0%	4.1%	4.7%	5.5%	4.2%	4.7%
24	0.2%	0.3%	0.8%	1.8%	0.6%	1.7%
36	0.0%	0.0%	0.3%	0.8%	0.1%	0.9%
60	0.0%	0.0%	0.1%	0.3%	0.0%	0.4%
120	0.0%	0.0%	0.0%	0.1%	0.0%	0.2%

Given the limited data on survival from the BEACON CRC trial, the ERG obtained data related to survival for patients with BRAF V600E mCRC from other RCTs or observational studies identified in the company's SLRs or through ERG's additional searches. The additional data identified are summarised in Table 49.

Table 49. Survival data from RCTs and observational studies for previously treated patients with BRAF mutant mCRC

Study & country	Design	Line of therapy	Intervention	Sample size	Median OS (95% CI), months	Median PFS (95% CI), months	OS % survival (95% CI)	PFS % survival (95% CI)
BEACON CRC [16] International	RCT	2 or 3 2 or 3	Encorafenib + cetuximab FOLFIRI or IRIN + cetuximab	220 221	9.30 (8.05 to 11.30) 5.88 (5.09 to 7.10)	4.27 (4.07 to 5.45) 1.54 (1.48 to 1.91)	1 year: [redacted] 1 year: [redacted]	[redacted] [redacted]
Peeters 2010/2015 [26] International	RCT	2	FOLFIRI FOLFIRI + panitumumab	45[a] NR[a]	5.7 4.7	1.8 2.5	NR NR	NR NR
RAISE [27] International	RCT	2	FOLFIRI FOLFIRI + ramucirumab	21 20	4.2 9.0	2.7 5.7	NR NR	NR NR
VELOUR [28] International	RCT	2	FOLFIRI FOLFIRI + (Ziv)-aflibercept	36[b] NR[b]	5.5 10.3	NR NR	NR NR	NR NR
de LaFouchardiere et al. 2019 [44] France	Obs	2	Irinotecan-based (44%) and oxaliplatin-based 919%) chemotherapy	Unclearc	NR	3.0 (2.6 to 3.9)	NR	1 year: 12.4 (7.5 to 18.5) 2 years: 2.3 (0.6 to 6.1)
Morris et al. 2014 [9] USA	Obs[c]	2 3	Irinotecan-based (39/58) NR	58 31	NR NR	2.5 (1.8 to 3.0) 2.6 (1.0 to 4.2)	NR NR	1 year 5%; 2 year 0% 1 year 0%

[a] 45 patients in total across the two trial arms. The ERG noted that despite a reported HR for OS of 0.64 (0.32 to 1.28) for panitumumab + FOLFIRI versus FOLFIRI, the reported median OS was shorter for the panitumumab + FOLFIRI arm than for the FOLFIRI arm (4.7 vs. 5.7 months).

[b] 36 patients in total across the two trial arms.

[c]Total number in the cohort 287, but this included patients receiving different lines of treatment.

[c] Authors stated that 28/39 patients treated with irinotecan as the second-line therapy concomitantly received an anti-EGFR (cetuximab or panitumumab), and that no difference in PFS was observed between those treated with an anti-EGFR and those without.

NR: not reported; Obs: observational.

The values of Table 49 suggest that the values for FOLFIRI median OS and PFS taken from the wider literature are not particularly different from those of the BEACON control arm. This can be read alongside the company OS estimates of Table 43 which suggest that FOLFIRI OS is substantially below the BEACON control arm OS, whereas the ERG values of Table 44 are much more closely aligned with the BEACON control arm OS. Similarly, the company PFS estimates of Table 47 suggest minimal PFS with FOLFIRI, whereas the ERG estimates of Table 48 are much better aligned with the BEACON control arm.

5.6 ERG additional analysis

5.6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG makes the following changes to the company base case:

- ERG01: Applies the ERG piecewise OS parameterised curves estimated using the BEACON trial data, using the exponential for its revised base case
- ERG02: Applies the BEACON trial PFS KM curves
- ERG03: Applies the BEACON FOLFIRI + cetuximab quality of life values for FOLFIRI
- ERG04: Applies the BEACON trial median relative dose intensities
- ERG05: Assumes an initial loading dose for cetuximab, with the subsequent maintenance dose being on day 8, and thereafter fortnightly
- ERG06: Revises the FOLFIRI grade 3+ AE costs to be based upon BEACON, with an estimated [redacted] average cost per patient while also correcting the cell referencing error in the model implementation, the joint effect being to increase the FOLFIRI grade 3+ AE cost within the model
- ERG07: Revises PFS monthly resource use to have no additional administration costs, one OP consultation and for FOLFIRI two district nurse visits
- ERG08: Makes some minor corrections to the direct drug costs.

The ERG undertakes the following sensitivity analyses:

- SA01: Applies the alternative ERG OS functional forms
- SA02: Applies the ERG PFS parameterised curves
- SA03: Applies the Peeters et al HRs to the BEACON control arm ERG OS exponential curve and PFS KM curves
- SA04: Applies the company ITC HRs to the BEACON encorafenib + cetuximab arm ERG OS exponential curve and PFS KM curves

- SA05: Explores the alternative company parameterised curves functional forms, adopting the same form for OS and PFS
- SA06: Equalises PFS quality of life values and PPS quality of life values between the arms at the BEACON trial averages
- SA07: Applies the TA405 CORRECT trial PPS QoL value of 0.59
- SA08:100% relative dose intensities, and BEACON mean relative dose intensities
- SA09: Assumes no IV drug vial sharing
- SA10: Increases the PPS treatment costs in the encorafenib + cetuximab arm proportionate to the increase in PPS relative to FOLFIRI.

The central probabilistic results of both the company base case, section 5.1, Table 36, and the ERG base case, section 5.6.3, are reasonably well aligned with their respective deterministic analyses. The ERG has no reason to think that this will not also be the case for the ERG sensitivity analyses.

5.6.2 ERG preferred assumptions: individual and cumulative effects

The individual effects that the ERG preferred assumptions have upon the company base case are presented in Table 50.

Table 50. ERG's preferred assumptions: ICERs versus FOLFIRI

Preferred assumption	ERG Section	ICER
Company base-case	5.1	£109k
ERG01: ERG piecewise OS parameterised curves: exponential	4.3.3.2	£214k
ERG02: PFS KM curves	4.3.3.3	£102k
ERG03: BEACON FOLFIRI+cetuximab QoL for FOLFIRI	4.3.3.11	£113k
ERG04: BEACON median RDIs	4.3.3.16	£112k
ERG05: Cetuximab loading dose, then 1st maintenance dose on day 8	4.3.3.13	£111k
ERG06: BEACON FOLFIRI+cetuximab SAEs for FOLFIRI	4.3.3.22	£109k
ERG07: PFS resource use revisions	4.3.3.20	£110k
ERG08: Minor drug cost corrections	4.3.3.19	£110k
ERG assumptions: cumulative effect	..	£242k

5.6.3 ERG exploratory and sensitivity analyses cost effectiveness estimates

The following results apply list prices for all treatments. The confidential cPAS appendix presents the corresponding analyses that include the encorafenib and comparators confidential patient access schemes' (PAS) price reductions on their list prices.

Table 51. ERG deterministic base case: cost estimates

	FOLFIRI	ENCO+c	net
Treatment costs	£215	£51,874	£51,659
Administration cost	£2,157	£3,578	£1,422
AE cost	[redacted]	£78	-£512
Subsequent treatment	£1,187	£907	-£280
Health state costs	£2,434	£3,015	£581
Terminal care cost	£6,965	£6,877	-£88
Total	£13,548	£66,329	£52,781

Table 52 reports the undiscounted months survival by health state, net effects.

Table 52. ERG deterministic base case: undiscounted months survival

	PFS	PPS	Total
FOLFIRI	4.3	5.5	9.8
Encorafenib + cetuximab	7.2	7.2	14.4
Net	2.9	1.7	4.5

The ERG revised base case estimates a somewhat smaller net overall survival gain. The OS gain is also mainly in PFS, though there is some PPS gain. The latter is broadly aligned with the very rough ERG calculations that examined an assumption of the same PPS among those surviving measured progression but more surviving measure progression in the encorafenib + cetuximab arm.

Table 53 reports the discounted QALYs by health state, and the pairwise net loss for the comparators relative to encorafenib + cetuximab.

Table 53. ERG deterministic base case: discounted QALYs

	PFS	PPS	Total
FOLFIRI	0.262	0.308	0.571
Encorafenib + cetuximab	0.436	0.353	0.789
Net	0.174	0.044	0.218

Table 54 presents the cost effectiveness estimates.

Table 54. ERG deterministic base case: pairwise incremental costs, QALYs and ICERs

	Costs	QALY
FOLFIRI	£13,548	0.571
Encorafenib + cetuximab	£66,329	0.789
Net	£52,781	0.218
ICER	£242,178	

Table 55 presents the probabilistic model central estimates running the model over 10,000 iterations. Note that this treats the direct drug costs deterministically, which the ERG thinks the more correct approach. Due to there not being a measure of uncertainty for the FOLFIRI specific quality of life values the ERG also treats quality of life values deterministically. This will understate the degree of uncertainty around the estimates to some degree, but due to the company probabilistic central cost effectiveness estimate being closely aligned with the deterministic estimate and the associated quality of life sampling being symmetric, the ERG does not think it will lead to bias in the probabilistic central cost effectiveness estimate.

Table 55. ERG probabilistic base case: pairwise incremental costs, QALYs and ICERs

	Costs	QALY
FOLFIRI	£13,627	0.572
Encorafenib + cetuximab	£65,026	0.790
Net	£51,399	0.218
ICER	£235,830	

The probabilistic model run over 10,000 iterations estimates similar central net costs and QALYs as the deterministic model, and the probabilistic central cost effectiveness estimate is similar to the deterministic estimate. The probabilistic model estimates that there is 0% probability of encorafenib + cetuximab being cost effective at all willingness to pay thresholds up to £100k per QALY and as a consequence the ERG does not present the CEAC.

The ERG sensitivity analyses cost effectiveness estimates are presented in Table 56.

Table 56. ERG sensitivity analyses: Encorafenib + cetuximab vs FOLFIRI

Analysis	ICER £/QALY
Base case	£242k
SA01a: ERG OS Weibull piecewise from 3 months	£227k
SA01b: ERG OS Gompertz piecewise from 3 months	£139k
SA01c: ERG OS Log-normal piecewise from 3 months	£202k
SA01d: ERG OS Log-logistic piecewise from 3 months	£201k
SA01e: ERG OS generalised gamma piecewise from 3 months	£206k
SA02a: ERG PFS exponential piecewise from 2 months	£245k
SA02b: ERG PFS Gompertz piecewise from 2 months	£258k
SA02c: ERG PFS Log-normal piecewise from 2 months	£280k
SA02d: ERG PFS Log-logistic piecewise from 2 months	£277k
SA02e: ERG PFS generalised gamma piecewise from 2 months	£254k
SA03: HRs applied to BEACON control arm to estimate FOLFIRI	£142k
SA04: HRs applied to BEACON encorafenib arm to estimate FOLFIRI	£149k
SA05a: Company Log-logistic curves for OS and PFS	£242k
SA05b: Company Weibull curves for OS and PFS	£257k
SA06: Quality of life values not arm specific	£212k
SA07: TA405 PPS QoL value of 0.59	£215k
SA08a: 100% relative dose intensities	£251k
SA08b: BEACON mean relative dose intensities	£236k
SA09: No vial sharing	£265k
SA10: Encorafenib + cetuximab PPS cost proportionate to time in PPS	£243k

The main sensitivity in terms of the ERG parameterised OS curves is to whether the Gompertz is applied. As previously noted the Gompertz results in considerably longer modelled survival in the encorafenib + cetuximab arm with 6% remaining alive at 10 years, compared to around 3% for the log forms and effectively none for the other functional forms.

Applying the ERG PFS parameterised curves rather than the BEACON KM PFS curves tends to worsen the cost effectiveness of encorafenib + cetuximab. It is likely that this is mainly due to the parameterised curves extrapolating a PFS tail for the control arm to a similar point as the encorafenib + cetuximab arm, when the BEACON PFS data for the control arm only extends to 13 months with [redacted] remaining in PFS, compared to extending to 21 months with [redacted] remaining in PFS in the

encorafenib + cetuximab arm. The ERG base case that applies the BEACON KM PFS curves artificially curtails PFS, but the ERG thinks that this is probably minor.

Whether the relevant hazard ratios are applied to the BEACON control arm curves or to the BEACON encorafenib + cetuximab arm curves is relatively unimportant. Both result in considerable improvements to the cost effectiveness estimate.

The company log-logistic curves result in much the same cost effectiveness estimate as the ERG base case. The main difference from the company base case is that the hazard ratios are not applied. In this context, applying the company Weibull curves only modestly worsens the cost effectiveness estimate. Applying the same PFS quality of life value to both arms and the same PPS quality of life value to both arms moderately improves the cost effectiveness estimate. This needs to be read in conjunction with the ERG base case applying the BEACON FOLFIRI + cetuximab specific PPS quality of life value for FOLFIRI, which improves the total QALYs in the FOLFIRI arm.

Applying the TA405 PPS quality of life value improves the cost effectiveness estimate. Given the longer time spent in PPS in the encorafenib + cetuximab arm this may seem counterintuitive. But as in SA06 which equalised the quality of life values between the arms, this has a greater effect upon the FOLFIRI PPS quality of life value compared to the encorafenib + cetuximab quality of life value. Changing the relative dose intensities to 100% and to the company base case BEACON mean values is not particularly influential.

If vials are not shared the cost effectiveness estimate worsens by a reasonable amount. As already noted, ERG expert opinion is that vial sharing will occur where possible, but it will be less than perfect and there will be wastage. As a consequence, the true effect of partial vial sharing with some wastage will lie somewhere between the ERG revised base case and SA09.

Increasing the PPS costs in the encorafenib arm to be proportionate to the increase in the time spent in PPS only slightly worsens the cost effectiveness estimate. But it should be noted that in this scenario the subsequent average treatment costs are virtually the same between the arms, whereas the revised base case suggests that encorafenib + cetuximab will result in average PPS treatment cost savings of £280. This seems counterintuitive. It arises due to PPS costs being applied per PPS incident patient rather than to the time spent in PPS, and the partitioned survival model possibly being poor at modelling incident PPS patients.

5.7 Conclusions of the cost effectiveness section

In line with TA405 and its FAD and ERG expert opinion, the ERG thinks that trifluridine + tipiracil tends to be used later in mCRC than the position that would most likely be occupied by encorafenib + cetuximab. But if trifluridine + tipiracil is a comparator, the ERG thinks that the naïve comparison using RECOURSE trial data is invalid. This is due to the lack of comparability between the trial populations i.e. the much higher number of previous treatments in the RECOURSE trial than in the BEACON trial.

ERG expert opinion is that cetuximab is not effective among BRAF V600E mutant patients, and that the BEACON trial was designed prior to this becoming apparent. The ERG cannot categorically state that cetuximab has no effect among BRAF V600E mutant patients. But the ERG thinks that the best available estimate for FOLFIRI PFS and OS is the BEACON control arm, without any hazard ratios being applied to remove the clinical effect of cetuximab.

It can also be noted that there is the suggestion that single agent irinotecan may not be as good and may not be as well tolerated as FOLFIRI. From this perspective, basing the effectiveness of FOLFIRI upon the BEACON pooled control arm may tend to favour encorafenib + cetuximab.

The ERG thinks that PFS is best and most simply modelled by using the BEACON PFS KM curves. But this may slightly artificially curtail the PFS curves. They are not quite complete and some patients remain censored by the data cut off date. The ERG parameterised PFS curves slightly worsen the cost effectiveness estimates.

Time to treatment discontinuation and PFS may not be entirely synonymous. There is some suggestion within the BEACON trial data that encorafenib + cetuximab use may tend to extend slightly beyond progression, while the reverse may have been the case in the control arm. If so, the cost effectiveness estimates may be biased in favour of encorafenib + cetuximab.

The base case cost effectiveness estimates of both the company and the ERG are slightly biased in favour of encorafenib + cetuximab due to the assumption of perfect vial sharing and no wastage. The true effect of less than perfect vial sharing will be between the base case and a scenario that assumes no vial sharing.

Neither the company nor the ERG consider treatment waning, in part due to the difficulty of implementing it within the company model structure.

The company electronic model presents cost effectiveness estimates for company piecewise curves that are somewhat worse than those of the company base case. These estimates are not presented in the written submission and there is no further information available about them.

5.8 End of life

The BEACON CRC trial reported a median OS of 9.30 months (95% CI 8.05 to 11.30) for encorafenib + cetuximab compared with 5.88 (95% CI 5.09 to 7.10), representing an improvement in median OS of 3.4 months. As described in Section 3.2.7, the ERG identified risk of bias to be unclear or high in several domains for the trial, and therefore there are some uncertainties with regard to the magnitude of improvement.

The company base case modelling estimates a mean undiscounted overall survival for FOLFIRI of 7.1 months, compared to 9.8 months in the ERG revised base case. The company base case estimates an undiscounted mean overall survival net gain of 10.1 months from encorafenib + cetuximab, compared to 4.5 months in the ERG revised base case. Both the company and the ERG estimates fall within the NICE end of life criteria. This also applies to the scenario analyses (SA01) that apply the alternative ERG OS parameterised curves.

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7 APPENDICES

7.1 Appendix 1 Detailed critiques of search strategies in company SLRs and ERG's additional searches for clinical effectiveness and cost-effectiveness evidence

Detailed critiques of search strategies for company SLRs for clinical evidence
Searches were undertaken in February 2019 and updated in September 2019. An appropriate selection of databases was used, as well as hand-searching of proceedings of cancer-related conferences, guidelines, systematic reviews and technology assessments.

The CS states that: "The search strategies considered the fact that there may be relevant trials that include patients with the specified mutation (RAS wild-type or BRAF V600) and terms for these mutations may not be present in the title, abstract or indexed terms" (CS Document B Appendices, page 4), and that: "The systematic reviews had a broad scope covering all lines of therapy across mCRC, irrespective of the genetic status;" (CS Document B, page 20). However, the ERG considers these statements to be inaccurate, as the searches in Medline, Embase and Cochrane Central incorporate thesaurus terms and free-text keywords for and BRAF and, in some cases, RAS. Some studies may have undertaken sub-analyses by genetic mutation status, and the terms for these may only be visible in the reporting article's full text, not in any indexed fields. To truly take into account that terms for the mutations may not be present in title, abstract or indexes, and ensure no relevant studies are missed in this way, the best approach would be a broad search for treatments of unresectable or metastatic colorectal cancer without specifying genetic mutation terms in the search strategy. Full text screening would identify whether outcomes for the BRAF mutation population were reported separately.

The ERG considers it possible that a small number of studies of comparator drugs may have been missed by the SLR searches, due to omission of search terms for drug type, class, or drug treatment in general (as opposed to names of specific drugs), exclusion of conference abstracts from the Embase searches, lack of a search of clinical trials registries (other than Cochrane CENTRAL) for the RCT search, and use of restrictive filters (omitting terms such as meta-analysis, systematically, consensus or guidance) to identify systematic reviews and guidelines for hand-searching. However, it is unlikely that any studies were missed that could have contributed to an NMA or ITC.

According to Table 7 (CS Document B Appendices page 81), the non-RCT SLR includes "observational studies (prospective and retrospective)" but not "case series". Criteria for

distinguishing between these study types are not described. “Pilot studies” are also excluded, but it is not clear how these are identified, and larger pilot studies may have provided useful information.

Additional literature searches carried out by the ERG to locate clinical effectiveness evidence

In order to assess the likelihood of the clinical effectiveness SLRs having missed any key studies in the mCRC with BRAF mutation population, the ERG undertook two searches on 25th March 2020 using Google Scholar, combining terms for BRAF, colorectal cancer, and drug treatments:

Search string 1:

BRAF colorectal cancer drugs OR chemotherapy OR immunotherapy OR folfiri OR folfox OR folfoxiri OR fluorouracil OR capecitabine OR bevacizumab OR cetuximab OR panitumumab

Search string 2:

BRAF colorectal cancer aflibercept OR ramucirumab OR regorafenib OR tipiracil OR trifluridine OR masitinib OR napabucasin OR atezolizumab OR pembrolizumab OR raltitrexed OR tegafur OR uracil OR irinotecan

In both cases, the first 50 results were screened. Two studies not identified by the company’s searches were found, however one of these would not have met the company’s eligibility criteria (CS Document B Appendices, pages 79-81), due to being a pilot study of fewer than 20 patients.[45] The other met the inclusion criteria for the non-RCT SLR, but did not compare treatments, so would not have been considered for inclusion in an NMA.[46] The ERG therefore concludes that it is unlikely that any studies were missed that could have contributed to an NMA or ITC.

Additional searches carried out by the ERG to locate health technology assessments and cost-effectiveness studies

In order to assess the likelihood of the company cost-effectiveness SLR having missed any key studies, the ERG undertook three Google searches on 25th March 2020:

Search string 1:

Colorectal cancer health technology assessment -screening

Search string 2:

health technology assessment colorectal cancer treatment

Search string 3:

cost effectiveness colorectal cancer metastatic OR unresectable OR advanced OR refractory

The first 50 results of each search were screened. Findings of the searches are presented in Section 4.1.2.

7.2 Appendix 2 Risk of bias assessment for key trials included in CS

Table 57 Risk of bias assessment of BEACON CRC trial

NICE checklist item (domain of bias)[a, b]	The company judgement and rationale	ERG judgement and rationale
Was randomisation carried out appropriately? (Yes/No/Not clear/NA)	Yes. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a computerised central randomisation list using an IWRS	Yes. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a computerised central randomisation list using an IWRS [Document B; B.2.4.4.4. method of randomisation; page 26].
	Low RoB	Low RoB
Was the concealment of treatment allocation adequate? (Yes/No/Not clear/NA)	Yes. See above	Yes. The randomisation schedule was created and managed by a third-party vendor, and treatments were assigned according to a computerised central randomisation list using an IWRS [Document B; B.2.4.4.4. method of randomisation; page 26].
	Low RoB	Low RoB
Were the groups similar at the outset of the study in terms of prognostic factors? (Yes/No/Not clear/NA)	Yes. Baseline characteristics were balanced between the groups.	No. Higher proportion of female patients in the control arm (n=127; 57.5%) vs. treatment arm (n=105; 47.7%). Higher proportion of Asian patients in the control arm (n=39; 17.6%) vs. treatment arm (n=25; 11.4%). More patients with left/right colon primary tumour location in control arm (n=22; 10%) vs. treatment arm (n=11; 5%) [Document B; B.2.4.11 Baseline characteristics and demographics, Table 4; page 34].

Were the care providers, participants and outcome assessors blind to treatment allocation? (Yes/No/Not clear/NA)	No. This was an open-label trial. To minimise bias, the Sponsor and their designee trial team, and the independent review committee were blinded to patient treatment assignment. The randomisation schedule was created and managed by a third-party vendor and treatments were assigned according to a central randomisation list using the IWRS.	No. This was an open-label study: investigators, some study personnel, and patients knew the study treatment assigned. Their knowledge would have influenced the outcomes of interest, especially subjective outcomes such as quality of life and other PRO measures [Document B; B.2.4.4.5. Blinding; page 27].
	Low RoB	High RoB
Were there any unexpected imbalances in drop-outs between groups? (Yes/No/Not clear/NA)	No. Discontinuation rates for any reason were similar across study arms. The majority of discontinuations across all arms were due to disease progression.	Yes. The losses to follow-up were similar across the groups (0.9% vs. 0.5%) [Table 1; ARRAY-818-302 CSR addendum, page 10]. There were substantially more patients not treated in the control arm (n=28; 13%) vs. treatment arm (n=4; 2%) [Figure 3; Document B Appendices; page 111]. Reasons behind this were withdrawal of consent or patient decision for the majority of cases in the control arm (23/28). The ERG notices in the CSR of the BEACON CRC (p. 167) that [redacted] As performance state is a strong predictor for survival, this might lead to bias in favour of treatment arm. Tumour follow-up assessments discontinued more often in control arm (n=211; 95.5%) vs, treatment arm (n=191; 87%).

		At cut-off of 15 August of 2019 (FAS data-set), there were fewer patients with ongoing treatment in control arm (n=7; 3.2%) vs. treatment arm (n=30; 13.6%) [ARRAY-818-302 CSR addendum; Table 14.1-1.3.1; page 62]. Treatment median duration was shorter in the control arm (7 weeks) vs. treatment group (19.3 weeks). Only a small percentage of patients in the Control arm (n=4; 2.1%) received ≥ 52 weeks of study treatment vs. treatment group (n=15; 7%). This discrepancy is not readily explained [Table 3; ARRAY-818-302 CSR addendum].
	Low RoB	High RoB
Is there any evidence to suggest that the authors measured more outcomes than they reported? (Yes/No/Not clear/NA)	No.	No. The BEACON study protocol (v. 7.0) and the clinical study reports for PROs [August update PRO tables and figures 3rd February 2020] and efficacy outcomes [ARRAY-818-302 (BEACON) CSR Addendum 15AUG Cutoff_Final Publish] were crosschecked for consistency. All the outcomes pre-specified in the protocol (v. 7.0) were reported in the results sections of the respective reports (i.e., no outcomes are suppressed). There were no outcomes reported in the results that were not pre-specified in the protocol.
	Low RoB	Low RoB
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? (Yes/No/Not clear/NA)	Yes. Analyses were conducted on the FAS, consisting of all randomised Phase 3 patients. Following the intention-to-treat principle, patients were analysed according to the treatment arm and stratum they were assigned to at randomisation.	Yes. Analyses were conducted on the FAS, consisting of all randomised Phase 3 patients. Following the intention-to-treat principle, patients were analysed according to the treatment arm and stratum they were assigned to at randomisation [Document B; B.2.5.1 Populations analysed; page 36]. Note that imputation was not done for missing values.

	Low RoB	Low RoB
FAS=full analysis set; IWRS=interactive web response system; RoB=risk of bias		

National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template (2015) [online]. Available at: https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness#quality-assessment-of-the-relevant-clinical-effectiveness-evidence [Last accessed: 29/01/2019].

[b] Centre for Reviews and Dissemination. Systematic Reviews CRD's guidance for undertaking reviews in health care (2009) [online]. Available at: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf [Last accessed: 29/01/2019].

Table 58. Risk of bias assessment of Peeters et al. study 2010/2015

NICE checklist item (domain of bias)[a, b]	The company judgement and rationale[1]	ERG judgement and rationale[1-2]
Was randomisation carried out appropriately? (Yes/No/Not clear/NA)	Not clear. Method of generating the sequence of randomisation was not reported.	Not clear. Method of generating the sequence of randomisation was not reported.
	High RoB	High RoB
Was the concealment of treatment allocation adequate? (Yes/No/Not clear/NA)	Not clear. Method of allocation concealment was not reported.	Not clear. Method of allocation concealment was not reported.
	High RoB	High RoB
Were the groups similar at the outset of the study in terms of prognostic factors? (Yes/No/Not clear/NA)	Yes. Baseline characteristics were balanced between the groups.	Not clear. Distribution of baseline characteristics were presented only for the total sample (n=421), but not for the BRAF mutated subpopulation (n=45). Thus, it is unknown whether or not the baseline characteristics of the BRAF mutated subpopulation were balanced between the study arms.
	Low RoB	High RoB
Were the care providers, participants and outcome assessors blind to treatment allocation? (Yes/No/Not clear/NA)	No. This was an open-label trial.	No. This was an open-label trial.
	High RoB	High RoB
Were there any unexpected imbalances in drop-outs between groups? (Yes/No/Not clear/NA)	Not clear. Details regarding study withdrawals were not clearly reported.	Not clear. Details regarding study withdrawals were not clearly reported.
	High RoB	High RoB
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All specified outcomes were reported.	Both outcomes (OS and PFS) were pre-specified in the methods section of the primary publication of the trial (Peeters 2010).[2]

(Yes/No/Not clear/NA)	Low RoB	Low RoB
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? (Yes/No/Not clear/NA)	Yes. The efficacy analysis was done using ITT population.	Not clear. Not clear if ITT analysis was applied or if any patients were excluded from the analyses. Not clear how withdrawals and lost to follow-up were handled in the analyses.
	Low RoB	High RoB
FAS=full analysis set; IWRS=interactive web response system; RoB=risk of bias; OS=overall survival; PFS=progression free survival; ITT=intention-to-treat		

1. Document B Appendices [26]: Peeters M, Oliner KS, Price TJ, Cervantes A, Sobrero AF, Ducreux M, et al. Analysis of KRAS/NRAS Mutations in a Phase III Study of Panitumumab with FOLFIRI Compared with FOLFIRI Alone as Second-line Treatment for Metastatic Colorectal Cancer. Clin Cancer Res. 2015; 21 (24): 5469-79.
2. Document B Appendices [34]: Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. Journal of Clinical Oncology. 2010; 28 (31):4706-13.

[a] National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template (2015) [online]. Available at: https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness#quality-assessment-of-the-relevant-clinical-effectiveness-evidence [Last accessed: 29/01/2019].
[b] Centre for Reviews and Dissemination. Systematic Reviews CRD's guidance for undertaking reviews in health care (2009) [online]. Available at: http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf [Last accessed: 29/01/2019].

7.3 Appendix 3 Presentation of company's cost-effectiveness analysis for comparison against trifluridine-tipiracil

7.3.1 Model structure

The same model structure is used for the comparison with trifluridine + tipiracil.

7.3.2 Population

The company models the patient population of the BEACON CRC trial: BRAF V600E mutant mCRC patients who have failed at least one prior treatment.

7.3.3 Interventions and comparators

The company models three possible initial treatments for those in PFS:

- Encorafenib + cetuximab (ENCO+c);
- FOLFIRI: folinic acid + fluorouracil + irinotecan; and,
- Trifluridine + tipiracil (T&T).

The company assumes that of those who received encorafenib + cetuximab during their PFS and those who received FOLFIRI during their PFS, half would receive trifluridine + tipiracil during their PPS. In contrast, those who received trifluridine + tipiracil during their PFS are assumed to receive no further treatment during the PPS. The post progression treatment assumptions have no effect upon the modelled clinical estimates or quality of life. They only affect the drug and administration costs that are incurred.

7.3.4 Perspective, time horizon and discounting

The perspective and discounting are as per the NICE reference case. A time horizon of 10 years is applied. For the company base case, the proportions of patients modelled as remaining alive at 10 years are:

- 1.4% for encorafenib + cetuximab,
- 0.0% for trifluridine + tipiracil

7.3.5 Treatment effectiveness and extrapolation

The main clinical effects are estimated as follows:

- For encorafenib + cetuximab the company estimates parameterised OS and PFS curves from the BEACON trial encorafenib + cetuximab Kaplan Meier data. Based upon the information criteria the company applies and extrapolates using the log-logistic curve for both OS and PFS.

- For the trifluridine + tipiracil OS and PFS curves a naïve comparison is made. There is no linkage to any of the other clinical data.
  - The company estimates parameterised OS and PFS curves from the RECOURSE trial data. Based upon the information criteria the company applies and extrapolates using the log-logistic curve for both OS and PFS. The company assumes that these curves are for BRAF wild type mutation.
  - The company sources OS and PFS hazard ratios of 4.00 and 3.57 for BRAF V600E compared to BRAF wild type from Peeters et al [26]. If applies these to the RECOURSE trial log-logistic OS and PFS curves.

Adverse events rates are taken from the single treatment arms of the relevant three trials. These have no effect upon patient quality of life due to an assumption that the BEACON PFS quality of life values that are applied include these effects. Adverse events only affect costs, these mainly increasing for FOLFIRI and trifluridine + tipiracil, due to their higher rates of neutropenia, leukopenia and liver failure.

The details of this are presented in sections 4.2.7.1 to 4.2.7.6 below. If the above summary is sufficient, readers may wish to turn to section 4.2.8 on page 75 which summarises the quality of life data.

7.3.5.1 Treatment effectiveness: Encorafenib + cetuximab

The company fits parameterised curves to the BEACON encorafenib + cetuximab, exactly as for the comparison with FOLFIRI.

7.3.5.2 Treatment effectiveness: Trifluridine + tipiracil

The clinical effectiveness of trifluridine + tipiracil is estimated entirely separately from the other comparators. The company digitises and infers pseudo individual patient data (IPD) from the RECOURSE trial.[35] The company fits parameterised curves to this pseudo-IPD data, the information criteria of which are in Table 59.

Table 59. Trifluridine + tipiracil: RECOURSE parameterised curves' information criteria

	OS		PFS	
Curve	AIC	BIC	AIC	BIC
Exponential	2438.4	2442.6	2208.6	2212.9
Weibull	2369.8	2378.4	2147.0	2155.5
Gompertz	2408.5	2417.0	2206.2	2214.7

Log-normal	2371.4	2379.9	2016.8	2025.3
Gamma	2360.1	2372.9	2001.8	2014.6
Log-logistic	**2353.5**	**2362.0**	**2015.7**	**2024.3**

The company selected the log-logistic curve for both OS and PFS, though does not state why in CS Section B.3.3.1.4.2. The company pseudo-IPD and parameterised curves are presented in Figure 27 and Figure 28.

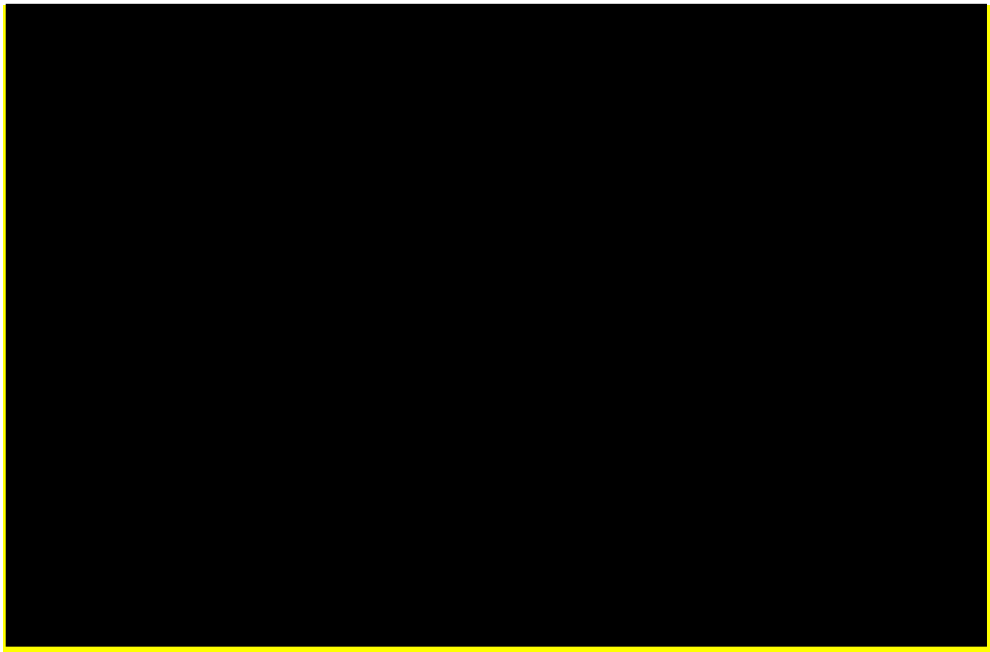


Figure 27. Company OS curves: Trifluridine + tipiracil: RECOURSE trial

The log-logistic curve has a reasonably good visual fit to the reconstructed Kaplan Meier curve.

Figure 28. Company PFS curves: Trifluridine + tipiracil: RECOURSE trial

The company states that it assumes that the RECOURSE trial is primarily among BRAF wild-type, but notes that BRAF mutation status is not explicitly reported in the cited paper.[35]

The company draws OS and PFS hazard ratios of 4.00 (2.78-5.56) and 3.57 (2.50-5.00) from Peeters et al.[26] and applies these to the RECOURSE trial curves, with effects upon the company base case log-logistic curves, labelled Applied, shown in Figure 29 and Figure 30.

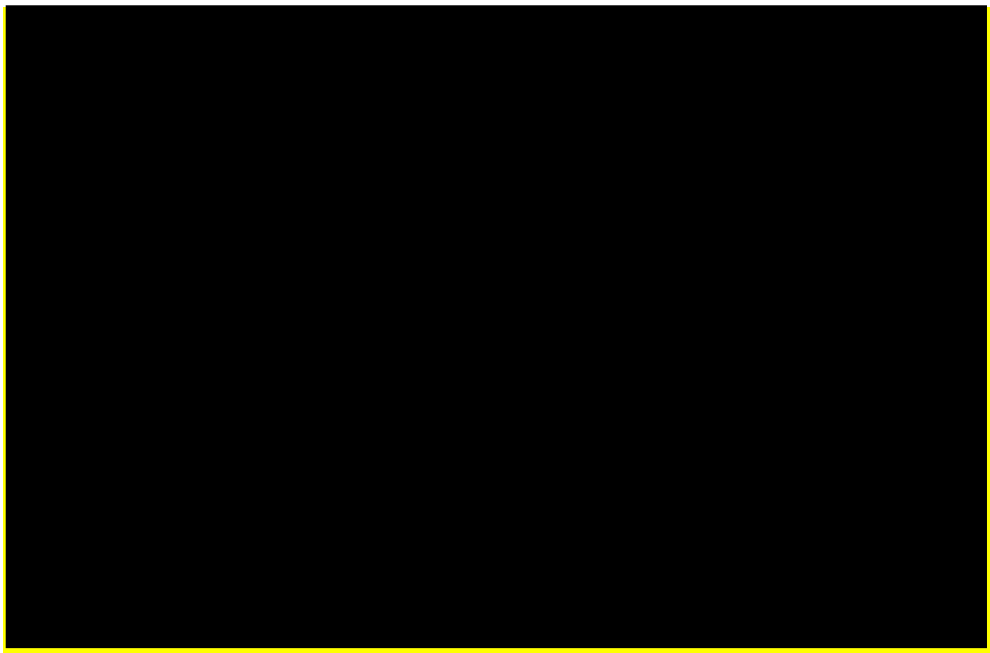


Figure 29. Company OS curves: Trifluridine + tipiracil

Figure 30. Company PFS curves: Trifluridine + tipiracil

The RECOURSE log-logistic curves have somewhat longer tails, particularly for OS. The application of the 4.00 OS hazard ratio and 3.57 PFS hazard ratio for BRAF v600 mutation compared to BRAF wild type considerably worsens both the OS and PFS, as shown by the "Applied" curves.

The parameterised curves' total undiscounted months OS, PFS and PPS within the 10 year time horizon, and the net gain from encorafenib + cetuximab relative to trifluridine + tipiracil, are presented in Table 17 below.

Table 60. Undiscounted months OS, PFS and PPS

	Absolute months survival			Encorafenib months net gain		
Months	OS	PFS	PPS	OS	PFS	PPS
BEACON: Encorafenib	16.8	7.4	9.4	..	..	..
T+T: RECOURSE	11.3	3.8	7.6	5.4	3.6	1.9
T+T: base case	4.0	1.9	2.2	12.7	5.5	7.3

Encorafenib + cetuximab is estimated to result in overall survival gains of 12.7 months compared to trifluridine + tipiracil. It is anticipated that the majority of the survival gains occurs after progression, when treatment with encorafenib + cetuximab is assumed to have stopped.

7.3.5.3 Treatment effectiveness: Time on treatment

As for the comparison with FOLFIRI, time on treatment for both arms is assumed to be the same as PFS.

7.3.6 Health related quality of life

7.3.6.1 BEACON quality of life values: PFS and PPS

The company applies the average BEACON EQ-5D values, differentiated by treatment arm and by PFS and PPS to arrive at the mean values of Table 18 below. Trifluridine + tipiracil is assumed to have the means of these values.

Table 61. Quality of life values: BEACON EQ-5D averages and T&T values

	Encorafenib + cetuximab	Control arm	T&T
PFS	0.743	0.741	0.742
PPS	0.622	0.631	0.627

7.3.6.2 Quality of life values: Age weighting

Age weighting is applied using the same method as for the comparison with FOLFIRI.

7.3.7 Resources and costs

7.3.7.1 Direct drug costs

The company calculated the direct drug costs on a 28-day basis due to the treatment cycles for cetuximab and FOLFIRI being 14 days, and 28 days for trifluridine + tipiracil. The 28-day cost is then increased pro rata to a monthly cost so as to be aligned with the model cycle length.

Oral encorafenib and oral trifluridine + tipiracil are treated similarly.

- The 28-day period requires four 75mg encorafenib tablets daily or 112 tablets in total, equivalent to 2.67 packs of 42 tablets. At a list price of £1,400 this is amounts to £3,733. Increasing this pro rata results in a monthly cost of £4,056.
- The 28-day period requires 10 trifluridine + tipiracil administrations, each requiring six 20mg tablets. Trifluridine + tipiracil is packaged as 60 units so is sufficient for 28 days, with a list price of £2,000. Increasing this pro rata results in a monthly cost of £2,173.

This results in the following direct drug and administration costs per monthly model cycle.

Table 62. Direct drug and administration costs: monthly model cycle

	ENCO+c	T&T
Drug: 1st cycle	£6,667	£2,173
Drug: subsequent cycles	£7,097	£2,173
Administration	£507	£17

7.3.7.2 Health state costs

The ongoing additional monthly resource use, unit costs and total monthly health state costs for trifluridine + tipiracil are the same as for encorafenib + cetuximab

Table 63. Additional ongoing monthly health state costs

	PFS			
	ENCO+c	T&T	PPS	Cost
Oral chemotherapy day case	0.50	0.50		£163
Medical oncologist OP visit	0.50	0.50		£227
GP home consultation			0.25	£100
Community nurse specialist visit			1.00	£37
Health home visitor	0.50	0.50	1.00	£46
District nurse visit (PICC line care)			1.00	£46
GP surgery visit			1.00	£28
Monthly cost	£218	£218	£182	

7.3.7.3 Inpatient costs

Adverse event rates are taken from the BEACON trial for encorafenib + cetuximab, and from Mayer et al[35] for trifluridine + tipiracil. Units costs are typically from NHS reference costs, though some adverse events have no cost applied due to company expert opinion. The influential unit costs are for neutropenia, taken from TA439, febrile neutropenia, taken from TA405, livery injury/failure, taken to be the average of NHS reference costs for liver failure codes GC01C, GC01D and GC01E. The adverse event rates, costs and mean cost by treatment arm are presented in Table 22 below.

Table 64. Adverse event rates and costs

	ENCO+c	T&T	Cost
Abdominal pain		2.4%	£145
Anaemia		18.2%	..
Asthenia		3.4%	£164
Cancer pain		0.0%	£145
Decreased appetite		3.6%	..
Diarrhoea		3.0%	£164
Fatigue		3.9%	£164
Febrile neutropenia		3.8%	£2,807
Hypertension		0.0%	£880
Intestinal obstruction		0.0%	£216
Leukopenia		21.4%	£2,504
Liver injury / failure		0.0%	£2,887
Nausea		0.0%	..
Neutropenia		37.9%	£2,504
Stomatitis		0.0%	£164
Thrombocytopenia		5.1%	£640
Urinary tract infection		0.0%	£216
Venous thrombosis		0.0%	£216
Vomiting		2.1%	£164
Mean total AE cost		£1,646	

Trifluridine + tipiracil is estimated to have somewhat higher adverse event costs than encorafenib + cetuximab. This is mainly driven by neutropenia and febrile neutropenia. There is effectively no neutropenia with encorafenib + cetuximab, but around 40% with trifluridine + tipiracil.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG response to company factual accuracy check

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

Warwick Evidence, 20 May 2020

Issue 1 Place in therapy appears to have been misunderstood

A number of locations related to this issue have been identified and for ease have been combined into one table.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12, Section 1.1 "Trifluridine-tipiracil was listed as a comparator in NICE's final scope and was included in the CS. ERG notes that while trifluridine-tipiracil is recommended (with no restriction regarding genetic mutation status) for previously treated metastatic colorectal cancer (mCRC) in NICE TA405, it is mainly used in clinical practice as a third- or subsequent-line treatment after two prior therapies failed or cannot be tolerated. It is therefore likely to be used in a later place in the treatment pathway compared with the proposed place for encorafenib, which could be started following one prior treatment." Page 14, Comparators	The text is both inaccurate and misleading and does not accurately reflect the potential positioning of encorafenib (Enco) with cetuximab as an alternative option to trifluridine-tipiracil for patients who have failed two prior regimens for advanced/metastatic disease. For accuracy the text should be amended to reflect the potential for Enco with cetuximab to be used instead of trifluridine-tipiracil as an alternative therapy. In addition, comparisons of Enco with cetuximab versus trifluridine-tipiracil should not be dismissed throughout the document.	The text appears to rule out encorafenib with cetuximab being used as a third-line agent instead of trifluridine-tipiracil, which is incorrect. As clearly stated in CS Form B.1.3.2.3 and acknowledged by the ERG in their report Section 2.2.2 (page 20), the company anticipate that Enco with cetuximab would enter the existing clinical pathway following first-line chemotherapy, as follows: • as an alternative option to FOLFIRI (in patients previously treated with FOLFOX at first-line) or • as an alternative option to trifluridine-tipiracil (in patients previously treated with FOLFIRI at second-line) or • as an alternative option to trifluridine-tipiracil (in patients previously treated with FOLFOXIRI at first-line). This would mean that replacing trifluridine-tipiracil as a third-line	The ERG does not rule out encorafenib dual therapy being used as a third-line agent instead of trifluridine-tipiracil. Nevertheless, given that encorafenib dual therapy is intended to be used as an alternative option to FOLFIRI as a second line therapy, and that none of current NICE guidelines includes a recommended systemic therapy specifically for BRAF V600E mCRC, it is very unlikely that encorafenib dual therapy (if recommended as a second-line therapy) will be withheld to be used as a third-line systemic therapy in this patient population. Furthermore, the ERG maintains that, given a complete lack of comparative evidence between encorafenib dual therapy and trifluridine-tipiracil in this specific patient population and place in the treatment pathway, no reliable assessment of relative clinical and cost-effectiveness is possible. To address the company's concern, the ERG has revised texts in the following

“Is trifluridine + tipiracil used at the same point of treatment as sought for encorafenib + cetuximab? The ERG considers that trifluridine + tipiracil is usually used later in the treatment pathway, and this is also supported by the TA405 final appraisal determination (FAD). • Is the naive comparison with trifluridine + tipiracil valid? This relies upon data from the RECOURSE trial for trifluridine + tipiracil. The ERG thinks that the much higher number of previous treatments in the RECOURSE trial compared to the BEACON trial invalidates this comparison.”		treatment would be a feasible position for the new regimen in clinical practice. This positioning is consistent with the evidence base from BEACON CRC in which people who previously received either one or two regimen(s) were included.	sections of the ERG report to highlight the company’s intention: Page 12, Section 1.1 “•Trifluridine-tipiracil was listed as a comparator in NICE’s final scope and was included in the CS. ERG notes that while trifluridine-tipiracil is recommended (with no restriction regarding genetic mutation status) for previously treated metastatic colorectal cancer (mCRC) in NICE TA405, it is mainly used in clinical practice as a third- or subsequent-line treatment after two prior therapies failed or cannot be tolerated. While the company suggested that encorafenib dual therapy could replace trifluridine-tipiracil as a third-line therapy in this context, the ERG considers that the technology (if recommended) is most likely to be used as a second-line therapy in clinical practice and is unlikely to be reserved as a third- or subsequent-line therapy, given that currently no other systemic therapy has been recommended in NICE guidelines for treating this specific patient population.”
Page 21, Comparators “The ERG notes that while trifluridine-tipiracil is recommended (with no restriction regarding genetic mutation status) for previously treated metastatic colorectal cancer (mCRC) in NICE TA405,15 it is mainly used in clinical practice as a third- or subsequent-line treatment after two prior therapies have failed or could not be tolerated. This comparator is therefore likely to be used in a place later in the treatment			Page 14, Comparators “• Is trifluridine + tipiracil used at the same point of treatment as sought for encorafenib + cetuximab? While the company suggested that encorafenib

pathway compared with the proposed place for encorafenib, which could be started after one prior treatment." Table 3, page 24 "ERG notes that trifluridine-tipiracil is mainly deployed in clinical practice as a third- or subsequent-line therapy. Therefore it may often be used in a place later in the treatment pathway compared with the proposed place for encorafenib dual therapy and may not be the most relevant comparator." Page 56 Section 3.6 "The ERG further notes that trifluridine-tipiracil is usually used as third- or subsequent line therapy, which occupies a later place in the treatment pathway compared with the place proposed for encorafenib dual therapy" Page 116, Section 5.7 "In line with TA405 and its FAD and ERG expert opinion, the ERG thinks that trifluridine +			dual therapy could replace trifluridine + tipiracil, which is recommended in TA405 as a third-line therapy for mCRC, the ERG considers that encorafenib dual therapy is most likely to be used as a second-line therapy, i.e. in a place earlier in the treatment pathway compared with trifluridine + tipiracil as described in Section 1.1." Page 22, Comparators "The ERG notes that while trifluridine-tipiracil is recommended (with no restriction regarding genetic mutation status) for previously treated metastatic colorectal cancer (mCRC) in NICE TA405,[15] it is mainly used in clinical practice as a third- or subsequent-line treatment after two prior therapies have failed or could not be tolerated. While the company suggested that encorafenib dual therapy could replace trifluridine-tipiracil in this context, the ERG considers that the technology is most likely to be used as a second-line therapy and therefore occupies an earlier place in the treatment pathway compared with trifluridine-tipiracil. Table 3, page 25 The ERG notes that trifluridine-tipiracil is mainly deployed in clinical practice as a third- or subsequent-line therapy. Therefore, while the company

tipiracil tends to be used later in mCRC than the position sought for encorafenib + cetuximab”			suggested that encorafenib dual therapy may replace trifluridine-tipiracil as a third-line therapy, the ERG discerns that the technology is most likely to be used as a second-line therapy given the lack of other recommended systemic therapy for this specific patient population, and therefore be used before trifluridine-tipiracil in the treatment pathway. Consequently, trifluridine-tipiracil may not be the most relevant comparator. Page 57, Section 3.6 “The ERG further notes that trifluridine-tipiracil is usually used as third- or subsequent line therapy. Therefore, while the company suggested that encorafenib dual therapy could replace trifluridine-tipiracil as a third-line therapy, the technology is most likely to be used as a second-line therapy in clinical practice and thus occupies an earlier place in the treatment pathway compared with trifluridine-tipiracil.” Page 117, Section 5.7 “In line with TA405 and its FAD and ERG expert opinion, the ERG thinks that trifluridine + tipiracil tends to be used later in mCRC than the position that would most likely be occupied by encorafenib + cetuximab.”

Issue 2 Further information required for balance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13, Section 1.2 "The ERG notes that the inclusion of cetuximab in both the intervention and control arms in the BEACON CRC study reflected the clinical uncertainty at the time of trial inception concerning the effectiveness of cetuximab (and epidermal growth factor receptor inhibitors, or anti-EGFRs, in general) in treating patients with BRAF V600E mutant mCRC."	The current statement is misleading and should be amended to provide necessary balance, to: "The ERG concludes that the inclusion of cetuximab in both the intervention and control arms in the BEACON CRC study reflected the clinical uncertainty at the time of trial inception concerning the effectiveness of cetuximab (and epidermal growth factor receptor inhibitors, or anti-EGFRs, in general) in treating patients with BRAF V600E mutant mCRC. The company noted that the choice of FOLFIRI or irinotecan in combination with cetuximab as the control arm represented one of the common therapeutic options among second- or third-line therapies in mCRC, consistent with European and US guidelines (European Society for Medical Oncology and National Comprehensive Cancer Network) at that time."	The current statement appears to be the interpretation of the ERG rather than a documented reason for the choice of cetuximab. As noted in the CS, the company suggest that the additional text should be added for necessary balance.	No factual error. However, the ERG agrees to revise the text based on company's proposed amendment: The ERG discerns that the inclusion of cetuximab in both the intervention and control arms in the BEACON CRC study reflected the clinical uncertainty at the time of trial inception concerning the effectiveness of cetuximab (and epidermal growth factor receptor inhibitors, or anti-EGFRs, in general) in treating patients with BRAF V600E mutant mCRC. The company stated that "the choice of FOLFIRI or irinotecan in combination with cetuximab as the control arm represented the most frequently used therapeutic options among second- or third-line therapies at the time of study initiation in global terms, consistent with European and US guidelines" (CS Document B, Section B.2.3, pages 21-22).

Issue 3 Potentially misleading information

A number of locations related to this issue have been identified and for ease have been combined into one table.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, Comparators "• Is the naive comparison with trifluridine + tipiracil valid? This relies upon data from the RECOURSE trial for trifluridine + tipiracil. The ERG thinks that the much higher number of previous treatments in the RECOURSE trial compared to the BEACON trial invalidates this comparison."	The statements appear unnecessarily dismissive of the approach taken by the company, given the paucity of data available for trifluridine-tipiracil and are lacking balance. We would recommend the statement is amended to give a more balanced view of the paucity of evidence available.	During the decision problem meeting, the company openly addressed the challenges they faced for this appraisal due to a paucity of evidence specifically in BRAF-mutant populations and highlighted that a naïve comparison was likely to be the only option available for comparisons with trifluridine-tipiracil. The ERG was open to this approach, acknowledging that the company should do the best they can with the evidence available, which has been done and submitted. The ERG concludes in its report that "the patient populations in the naïve indirect comparison were too heterogeneous to allow reliable comparison of data between these two trials." The company acknowledge the issues of uncertainty introduced when performing a naïve comparison but were mindful to provide a comparison rather than no comparison at all to aid the	The ERG appreciates the company's effort and does not criticise its approach given the paucity of evidence. The ERG simply highlights the lack of suitable evidence and the enormous uncertainty associated with the analysis presented. No factual error, no revision required.
Page 45, Section 3.3.2 "Consequently, the ERG considers that the trial populations were too different for indirect comparisons to be made and that using data from these two trials is likely to generate results that are unlikely to be valid. Even if taken at face value, the company's naïve comparison would likely to be biased in favour of encorafenib dual therapy due			

to the substantial difference in treatment history between the patients”		NICE committee in their decision making. In its report the ERG also suggests that the much higher number of previous treatments in the RECOURSE trial compared to the BEACON trial invalidates this naïve comparison, as this is likely to substantially bias in favour of encorafenib dual therapy. However, although survival curves aren’t available by line of therapy, interrogation of subgroup data from the RECOURSE trial shows that trifluridine-tipiracil is progressively more effective with later lines of therapy, and following two prior regimens where the encorafenib regimen could be used, trifluridine-tipiracil appears to be no better than best supportive care (placebo arm); the HR for OS with trifluridine-tipiracil vs placebo was 1.05 (95% CI: 0.68, 1.63) after two prior regimens, 0.74 (95% CI: 0.51, 1.08) after three prior regimens and 0.59 (95% CI: 0.47, 0.73) after four or more prior regimens. By contrast the effectiveness of Enco with cetuximab appeared to be consistent regardless of line of therapy (one prior or two prior regimens). Given the uncertainty, seeking expert clinical opinion as to the relative effectiveness of trifluridine-tipiracil and FOLFIRI may prove useful to the committee.	

Issue 4 Information missed in CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29, Section 3.1.1 "Quality assessment of seven of these studies are presented in CS Document B Appendices Table 6 (pages 69-70). It was not clear why quality assessment was not carried out for three of the trials."	The current statement is misleading and should be amended to: "Quality assessment of eight of these studies are presented in CS Document B Table 7 (page 45; BEACON CRC) and in CS Document B Appendices Table 6 (pages 69-70; comparator trials). Quality assessment was not carried out for the three remaining trials as these were only available as abstracts."	Quality assessments were presented for 8 of 11 studies rather than 7 as stated. This included BEACON CRC presented on page 45 of CS Form B and seven comparator trials in CS Form B Appendices Table 6. As stated on page 68 of CS document B Appendices, quality assessment was presented, provided a full study publication was available. Three studies presented as abstracts were not assessed for quality due to limited information.	The ERG accepts the company's proposed amendments.

Issue 5 Incorrect information from literature review

A number of locations related to this issue have been identified and for ease have been combined into one table.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29, Section 3.1.1 "In addition to the 11 RCTs that best match the decision problem in terms patient population and lines of treatment, the company also identified 52 RCTs reported in 75 publications/abstracts pertaining to first line treatment for patients with BRAF mutations."	Amend to: "In addition to the 11 RCTs that best match the decision problem in terms of patient population and lines of treatment, the company also identified 52 RCTs reported in 75 publications/abstracts pertaining to first line treatment for patients with mCRC (although not specifically with BRAF mutations). These were not further examined in the CS."	As described in the CS Form B appendices page 28, Section D.1.1.3.2, 52 distinct studies were identified by the SLR which reported on first-line therapies. As described in the PICOS CS Form B appendices page 22, Table 1, the population considered was broader than just those patients with BRAF mutations, namely "Adult patients (aged ≥18 years) with RAS wild-type (i.e. this includes also KRAS and NRAS wild-type) or BRAF V600 metastatic and/or irresectable colorectal cancer."	The ERG accepts the company's proposed changes.
Page 30, Section 3.1.2 "…given the very limited evidence for 2nd and subsequent lines of treatment in the BRAF V600E mutant mCRC population, the ERG also explored potentially useful data in the 52 RCTs pertaining to first line treatment in this population."	Amend to: "…given the very limited evidence for 2nd and subsequent lines of treatment in the BRAF V600E mutant mCRC population, the ERG also explored potentially useful data in the 52 RCTs pertaining to first line treatment in the broader mCRC population captured by the company systematic review."		

Issue 6 Incorrect information regarding literature review methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30, Section 3.1.2 "Overall the ERG found the study selection criteria and study selection process not well specified and not well matched for both SLRs. There were conflicting statements with regard to the data extraction process (CS Document B Appendices, pages 25 and 82) and inconsistent execution of quality assessment."	This statement is both inaccurate and misleading and should be removed.	Differences in study selection process relate to the population of interest and were very deliberate in their differences. Whereas the RCT search was broader than the indication for Enco with cetuximab, the purpose of the non RCT search was to find supplementary data specific to the indication and given the lower quality of evidence derived from observational studies was purposely limited to mCRC populations with BRAF mutations. Data extraction processes were identical between the RCT and non-RCT searches as described in the CS Form Appendices page 25 and 82 under the heading "data extraction". Justification for missing quality assessments for RCTs was reported (as raised under Issue 4) and quality assessment was not reported for non-RCTs since these studies were not used any further within the submission.	The ERG accepts the company's clarification for the processes of study selection and quality assessment, but maintains that the study selection criteria particularly with respect to intervention were not well specified (see CS Document B Appendices Table 1, pages 22-23; and Table 7, pages 79-80). Although the data extraction process was identical for both the RCTs and observational studies, the ERG noted conflicting statements regarding whether data extraction was carried out by one analyst and checked by another or independently by two analysts (see CS Document B Appendices, pages 25 and 82), Therefore the ERG statement on page 30 section 3.1.2 is amended to read: "Overall, the ERG is satisfied with the company's study selection process and quality assessment, although the ERG found the study selection criteria not very well specified

			and noted that there were conflicting statements with regard to the data extraction process (CS Document B Appendices, pages 25 and 82).

Issue 7 Potentially misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30, Section 3.2 "Although the company's SLR identified 11 potentially relevant RCTs, the CS focused on a single study (BEACON CRC trial)[16] that used the technology of interest (encorafenib with cetuximab) in people with BRAF V600E-mutant mCRC (CS Document B; pages 20-57)"	Amend to: "Although the company's SLR identified 11 potentially relevant RCTs investigating the intervention and/or comparators, the CS focused on a single study (BEACON CRC trial)[16] that used the technology of interest (encorafenib with cetuximab) in people with BRAF V600E-mutant mCRC (CS Document B; pages 20-57)"	The wording of the current statement suggests that 11 studies investigating encorafenib were identified of which only one was reported by the CS. In reality, the 11 studies reported on the intervention (encorafenib with cetuximab) or NICE comparators.	The ERG accepts the proposed amendment.

Issue 8 Further rationale required

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30, Section 3.2 "As alpelisib is not licenced for treating mCRC and is not a comparator of interest, the trial is only briefly examined in Section 3.5."	Amend to: "As alpelisib is not licensed for treating mCRC and is not a comparator of interest, and the dose of encorafenib investigated (200 mg QD) is lower than the recommended dose (300 mg QD), the trial is only briefly examined in Section 3.5."	The study in which Enco with cetuximab is compared with Enco with cetuximab + alpelisib investigated a 200 mg QD dose for encorafenib, which is inconsistent with the recommended dose (300 mg QD). This should be added as an additional rationale.	No factual error, but the ERG accepts the proposed amendment to enhance clarity.

Issue 9 Appropriate data cut not reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35, Section 3.2.2 "Among patients receiving the treatment (n=631), the rate of treatment discontinuation was higher in the control arm (n=156, 71%) vs. the dual therapy arm (n=138, 63%) (Appendix D; Figure 3, page 110-111). The contributory factors for this difference between the two arms were higher numbers of progressive disease, change in patient condition, death, and	Amend to: "Among patients receiving the treatment (n=631), the rate of treatment discontinuation was similar in the control arm (n=186, 84.2%) vs. the dual therapy arm (n=186, 84.5%) (Appendix D; Table 14, page 112-113). Specific reasons for discontinuation which occurred at different rates between the two arms were progressive disease, change in patient condition, death, and withdrawal of consent in the control arm."	Discontinuation data presented is for the earlier February 2019 data cut. Outcomes data (i.e. OS, PFS etc) for BEACON CRC is presented for the most mature dataset from August 15th, 2019 and thus for consistency the discontinuation rates for the August 2019 data cut should also be presented.	The ERG agrees that reporting results based on data cut-off 15 August 2019 would ensure better consistency. The text (including the preceding paragraph) has been revised to read: "The ERG noted that of patients allocated to the three treatment arms, 34 did not receive the treatment, of whom 28 (82%) were from the control arm. Specifically, more patients did not receive treatment in the control arm (28/221,13%) vs. the encorafenib with cetuximab arm (4/220, 2%),

withdrawal of consent in the control arm.”			most of them being due to withdrawal of consent. According to the company response (CR; Question A6, page 127): “*Randomised but not treated patients were followed-up for efficacy and safety measures until their study withdrawal, in the same way as other patients*.” The patients who were randomised, but not treated, were included in the FAS and the Response Efficacy Set (RES), but not in the Safety Set (SS) or the Per Protocol Set (PPS). For efficacy measures, randomised but not treated patients were censored using the same rules as for other patients (CR Question A6, page 127). Among patients receiving study treatment (data cut-off 15th August 2019), the rate of treatment discontinuation was higher in the control arm ([redacted] vs. the dual therapy arm ([redacted] (CS Document B Appendix D; Table 14, page 112). Specific reasons for discontinuation which occurred at different rates between the two arms were progressive disease, change in patient condition, adverse events/tolerability of treatment, death, withdrawal of consent and dose interruption.”

Issue 10 Missing data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 39, Section 3.2.5 “Regarding specific AEs (reported in >30% patients), the control arm experienced slightly higher rates of diarrhoea and dermatitis acneiform compared to the encorafenib with cetuximab arm.” “[redacted]”	Amend to: “Regarding specific AEs (reported in >30% patients), the control arm experienced higher rates of diarrhoea ([redacted]) and dermatitis acneiform ([redacted]) compared to the encorafenib with cetuximab arm.” [redacted]	Percentages for AEs over 30% should be presented to provide balance to the narrative; the current language of “slightly higher rates” does not elude to the ~10% absolute difference in rates of diarrhoea and dermatitis acneiform. The list of less frequent AEs provided by the ERG has also missed some additional all grades AEs that occur more frequently in the control arm that should be added for balance.	The ERG accepts the proposed amendment.

Issue 11 Misleading statement

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42, Section 3.2.8 "The ERG considers the sensitivity and subgroup analyses to be adequate, except between the subgroups of patients receiving different treatments (FOLFIRI or irinotecan) in the control arm. The BEACON CRC trial was not designed and powered to test these differences between the patient subgroups."	It is not clear what is meant by this statement and would benefit from some clarification text.	For clarity, subgroup analyses were not conducted for patients who received different treatments (FOLFIRI or irinotecan) in the control arm. The current wording suggests that these analyses were conducted but were somehow inadequate.	No factual error. The ERG now adds a further sentence to provide further clarity; "The ERG considers the sensitivity and subgroup analyses to be adequate, except between the subgroups of patients receiving different treatments (FOLFIRI or irinotecan) in the control arm, for which no subgroup analysis was reported by the company and for which the ERG carried out exploratory analyses using data supplied in CR to ERG clarification questions (see section 3.5.2.1)."

Issue 12 Missing information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 46, Section 3.4 "The assumption of equivalence between cetuximab and panitumumab was assumed since both drugs belong to the same class, i.e. EGFR inhibitors"	Amend to: "The assumption of equivalence between cetuximab and panitumumab was assumed since both drugs belong to the same class, i.e. EGFR inhibitors. The company state that NICE concluded during TA439 that cetuximab and panitumumab were likely to have similar effectiveness in treating RAS wild-type mCRC, an assumption that was supported by clinical experts consulted during that appraisal and further confirmed by experts consulted by the company for the current appraisal."	The current text suggests an assumption on the part of the company that was made without further substantiation. The suggested text reflects the full justification provided by in CS Form B page 63.	The additional statements are not specific to BRAF mutant mCRC, and therefore ERG considers them to be less relevant. No factual error, no revision required.

Issue 13 Potentially misleading information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 47, Section 3.4 "While the reported estimates of OS (HR=0.64, 95% CI: 0.32, 1.28) and PFS (HR=0.69, 95% CI: 0.32, 1.49) from the Peeters 2010/2015 trial suggested substantial survival benefit for adding panitumumab (and by extension, cetuximab according to the company's assumption) to	The concluding statement appears to suggest that Peeters 2010/15 may be an outlier and does not reflect the limitations of all data for anti EGFRs in BRAF-mutant populations – small sample sizes and large confidence intervals. We would recommend the statement is amended to reflect these limitations and in turn give a balanced view.	The conclusion of the ERG appears unbalanced and inconsistent, and could therefore be considered as somewhat misleading. The observation that the analyses from Peeters 2010/15 are underpowered to show significant differences between interventions is correct but this is true of all the evidence for anti-EGFRs in BRAF-mutant patients, which is likely to be driving the uncertainty around	The ERG maintains its interpretation of the evidence. No factual error; no revision required.

FOLFIRI compared with FOLFIRI alone, these analyses were very under-powered. The presumed substantial effects of panitumumab based on the point estimates are also incongruent with other evidence and consensus reported in the literature, which suggest little benefit of anti-EGFRs in this group of patients (see Section 3.5.2.2 below)"		how much benefit EGFRs have in this specific patient group. Rather than the findings of the Peeters study being incongruent with other evidence and consensus, the two meta-analyses specifically cited by the ERG (References 39 [Rowland] and 40 [Pietrantonio]), both show some numerical benefits of anti-EGFRs but with large confidence intervals driven by small sample sizes. This is reflective of the paucity of evidence available specifically in the BRAF population, as cited by the company in identifying and selecting evidence for consideration in the submission, and specifically in the ITC by way of a robust systematic review, in line with NICE process.	

Issue 14 Unnecessarily unbalanced narrative

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54, Section 3.5.4 "Data for OS were not sufficiently mature for the BEACON CRC trial at the data cut-off time of August 2019 reported in the CS, with 32.8% of the patients still being followed for survival (CS Document B Appendices Section D2.2, page 112). The ERG therefore compiled available survival data from other RCTs and observational studies conducted in previously treated patients with BRAF mutant mCRC, identified through the company's SLRs and the ERG's additional searches"	The statement appears unnecessarily dismissive of the BEACON CRC study and intimates that alternative data may prove to be of greater value. It would be helpful for the reader to understand why the ERG believe the OS data to not be sufficiently mature from BEACON CRC and how compiling information from generally smaller post-hoc subgroup analyses may be of help for validation purposes.	BEACON CRC is the first and only phase 3 study specifically designed and powered to investigate treatment differences in a BRAF-mutant population. By contrast other available evidence in BRAF-mutant populations is limited by much smaller sample sizes, are not powered to detect treatment differences and are generally post-hoc in nature.	The ERG has clearly stated that the data for OS were not sufficiently mature as nearly one-third of patients were still being followed for survival at data cut-off. No factual error; no revision required.

Issue 15 Potentially misleading information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 55, Section 3.6 "The impact of the adjustment made through the ITC based on these data would be likely to inflate the effectiveness of encorafenib dual therapy compared with FOLFIRI due to the presumed benefit of cetuximab/anti-EGFR in the BEACON control arm."	Amend to: "The impact of the adjustment made through the ITC based on these data may overly inflate the effectiveness of encorafenib dual therapy compared with FOLFIRI due to the uncertainty of the magnitude of benefit provided by cetuximab/anti-EGFR in the BEACON control arm."	The company acknowledge the uncertainty in how much benefit cetuximab may provide to the overall regimen and that the evidence base for anti EGFRs in BRAF-mutant populations consists of small sample sizes which generate estimates with wide confidence intervals. However, the company believe that the evidence does not allow the ERG to dismiss cetuximab as having no added benefit at all, but rather that there is some level of uncertainty as to how much benefit it provides. The existing statement within the ERG report is worded to question whether cetuximab has any benefit rather than questioning the size of the benefit; the company believe the latter would be more appropriate and balanced given the paucity of data and the uncertainty in the available data on this issue.	The ERG believes that its original wording better reflects the uncertainty related to the effects of cetuximab and anti-EGFRs and the impact of the data on the results of the ITC. No factual error; no revision required.

Issue 16 Missing information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63, Section 4.2.7 "Adverse events rates are taken from the single treatment arms of the relevant three trials."	Amend to: "Grade 3+ adverse event rates are taken from the single treatment arms of the relevant three trials."	The economic model incorporates AEs likely to have a notable impact on costs, namely those of severity Grade 3+ with an incidence of at least 2% in either the Enco with cetuximab arm of BEACON CRC, the FOLFIRI arm of RAISE or the trifluridine-tipiracil arm of the RECOURSE trial.	The ERG accepts the company proposed revision.

Issue 17 Incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 67, Section 4.2.7.2 "The company base case does not use any data from the BEACON control arm due to both FOLFIRI and irinotecan being used in conjunction with cetuximab."	Amend to: "Whilst the BEACON control arm data are not used directly to inform efficacy estimates in the base case, BEACON control arm data were included as a component of the ITC."	The wording in the ERG report is factually incorrect. The BEACON control arm was included in the ITC which was used to generate the hazard ratios used in the base case.	The ERG has revised the text to "The BEACON control arm informed the company ITC and resulting hazard ratio. But the company base case does not direct apply any of the Kaplan Meier data from the BEACON control arm or fit parameterised curves to this data, due to both FOLFIRI and irinotecan being used in conjunction with cetuximab."

Issue 18 Incorrect information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79, Section 4.3.3.1 "The company's modelling of OS and PFS for FOLFIRI + cetuximab results in considerable deviations from the observed data in the control arm of BEACON CRC"	The current statement is factually incorrect and should be amended to: "The company's modelling of OS and PFS for FOLFIRI results in considerable deviations from the observed data in the control arm of BEACON CRC"	The company modelled FOLFIRI, as per NICE scope rather than FOLFIRI + cetuximab. Consistent with this, the curves displayed in Figure 17 of the ERG report to which the sentence may refer appear to show the K-M curves for the BEACON CRC control arm, alongside the modelled curves for FOLFIRI used in the company base case.	The ERG accepts the company proposed revision.

Issue 19 Incorrect labelling of information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 80, Section 4.3.3.2 "An examination of the models fitted by the company in Figure 17 demonstrates how there is deviation of all curves from the observed data, between months 2 to 4 and months 8 to 10."	Amendment is required to either refer to a different figure (possibly Figure 5) or to amend the text, otherwise the reader cannot see the proposed deviation at months 2 to 4 and months 8 to 10.	Figure 17 of the ERG report appears to show the BEACON control arm K-M curves for OS and PFS and the FOLFIRI curves generated by applying the HR from the ITC to the BEACON CRC encorafenib curves. The figure does not show the parametric curves fitted to the BEACON data and how these curves deviate from the trial K-M curves. The appropriate figure from the ERG report might be Figure 5 "Company OS curves and KM data: BEACON encorafenib + cetuximab arm".	The ERG accepts the company proposed revision and the text is now referring to Figure 5.

Issue 20 Incorrect labelling of information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97, Table 30 Mean and median labels are transposed	Amend table to swap mean and median labels, such that mean row reports [redacted], while median row reports [redacted].	Table rows are labelled incorrectly.	The ERG accepts the proposed amendment.

Issue 21 AIC mark up

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101, Table 31 “IRIN+c” column	The “IRIN+c” column requires all data to be marked up as AIC.	This data is not in the public domain and should be marked as AIC, as per CR A13.	The ERG accepts the proposed amendment.

Issue 22 Incorrect labelling of information

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 101, Table 31 “BEACON SAEs” table header label	Amend to: “BEACON Grade 3+ AEs”	AE rates reported are for AEs of Grade 3 and above in severity, not serious AEs (SAEs) as labelled in the ERG report.	The ERG accepts the proposed amendment.
Page 101, text under table	Amend to:		

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"Unless cetuximab is protective against SAEs and in particular against neutropenia, the ERG thinks it is more consistent to apply the BEACON FOLFIRI + cetuximab mean SAE cost of [redacted] than the company base case estimate of £910."	"Unless cetuximab is protective against Grade 3+ AEs and in particular against neutropenia, the ERG thinks it is more consistent to apply the BEACON FOLFIRI + cetuximab mean AE cost of [redacted] than the company base case estimate of £910."		
Page 111, Section 5.6.1 "ERG06: Revises the FOLFIRI SAE costs to be based upon BEACON, with an estimated [redacted] average cost per patient while also correcting the cell referencing error in the model implementation, the joint effect being to increase the FOLFIRI SAE cost within the model"	Amend to: "ERG06: Revises the FOLFIRI AE costs to be based upon BEACON, with an estimated [redacted] average cost per patient while also correcting the cell referencing error in the model implementation, the joint effect being to increase the FOLFIRI AE cost within the model"		

Issue 23 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 106, Section 5.4 "The electronic copy of the company model contains ICERs	Suggested that this section is removed from the ERG report.	Reference to piecewise analysis in the Excel model refers to an exploratory approach undertaken which used K-M data for the duration of the trial followed by	No factual error, no revision required.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
for piecewise curves compared to the continuous parameterised curves presented in the CS"		parametric extrapolation for the remainder of the model time horizon. This approach was considered briefly using an early immature dataset from BEACON and was not explored further. The piecewise analyses were felt to deviate too far from the NICE reference case due to the difficulties inherent in the probabilistic modelling of raw Kaplan-Meier curves, as probabilistic modelling of curves is essential (NICE DSU TSD 14, Section 3.7[a]). In short, if this approach were taken, the raw Kaplan-Meier components of the piecewise curves would not be modelled probabilistically, whereas the extrapolated period would be. This was felt to place undue certainty in the trial data. The parametric models were therefore used by the company for the entire curves. Reference to the piecewise analysis was retained in the model in error and for the purposes of the company submission should be disregarded. We would also like to take this opportunity to raise some significant concerns around the revised	

[a] Latimer N. NICE DSU TSD 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		modelling approach offered by the ERG, which we plan to explore in more detail at the technical engagement step: 1. Visual inspection of Figure 19 shows that the ERG's approach appears to underestimate the OS of patients in the Enco with cetuximab arm between months 11 and 15. 2. Not utilising the survival data prior to 2.8 months appears to be arbitrary and does not have a clear rationale other than there is a change in the hazard function for Enco with cetuximab. It appears that no data from the FOLFIRI with cetuximab arm were used to inform this decision. Whilst NICE DSU TSD 14[a] advises that models which exclude outlying data should be considered, it also states that caution should be taken when excluding data, particularly if a large percentage of data points are excluded. It is not clear how the data prior to 2.8 months is used in the model. 3. Limiting AUC analyses to 16 months does not take into consideration clinical data gathered beyond this point. The company maintains that all	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		available data should be used to inform OS and PFS curves and that probabilistic sensitivity analysis is the appropriate manner to investigate the uncertainty associated with low numbers of patients at risk towards the end of the trial. 4. The company believe they took the simplest approach that adequately modelled the disease and the data available, while fulfilling the NICE reference case and the approaches outlined in NICE DSU TSDs, and also sought expert input from clinical and health economic experts to guide the approach and assumptions made. In contrast, it can be argued that the ERG may have taken an overly complex approach that may have caused over-fitting of the parametric curves to data beyond 2.8 months. It is also not clear how the data prior to 2.8 months was used.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it 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 appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

Commonly used abbreviations

BRAF	B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf
EGFR	Epidermal Growth Factor Receptor
FOLFIRI	Folinic acid plus 5-fluorouracil plus irinotecan
IRIN	Irinotecan
MAPK	Mitogen-Activated Protein Kinase
mCRC	Metastatic colorectal cancer
RAS	Family of related proteins which function as molecular switches in the MAPK pathway

1.1 Disease background

- Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer refers to disease that has spread beyond the large intestine and nearby lymph nodes.

- Approximately 10% of people with colorectal cancer have tumours with the BRAF V600E mutation, in which valine (V) is substituted by glutamic acid (E) at amino acid 600. B-Raf is a protein encoded by the BRAF gene and is involved in the RAS/MAPK pathway. Mitogen-activated protein kinase (MAPK) pathways control growth and cell proliferation.

- Prognosis is significantly poorer and greater risk of disease recurrence than for people with 'wild-type' ('normal' non-mutated) BRAF/RAS metastatic colorectal cancer.

- NICE clinical guideline 151 recommends testing for RAS and BRAF V600E mutations in all people with metastatic colorectal cancer suitable for systemic anti-cancer treatment.

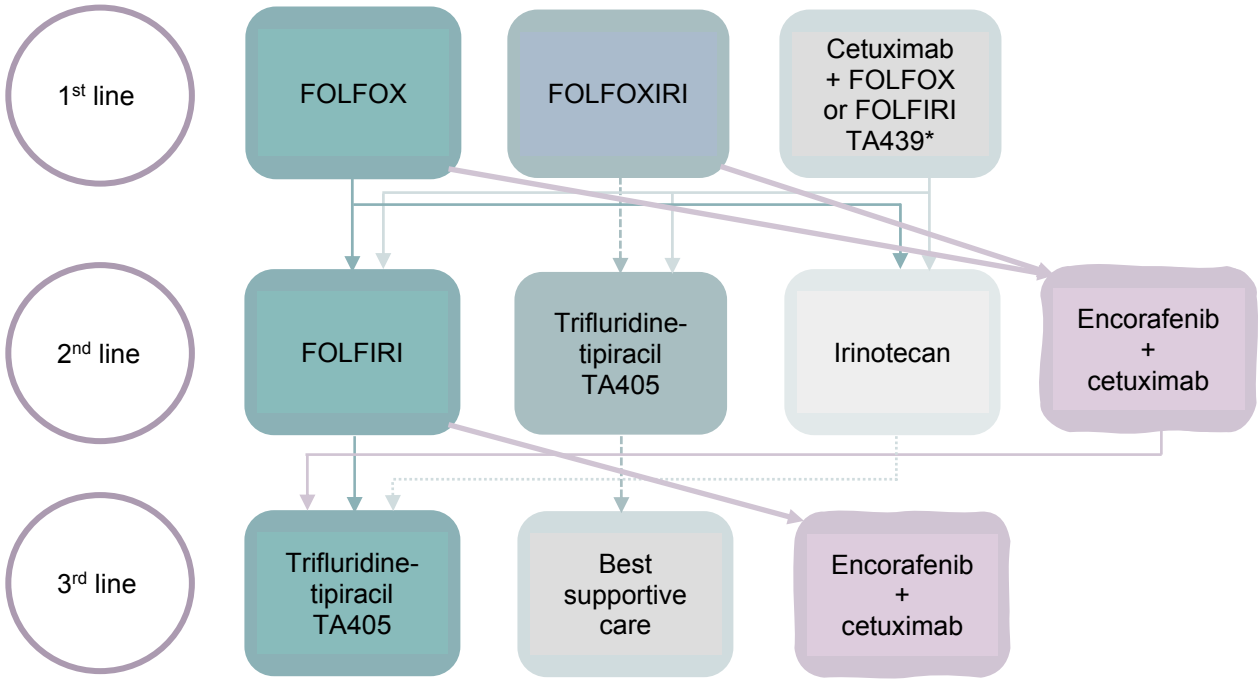
- The aim of treatment for metastatic colorectal cancer is to prolong survival and improve quality of life. There are currently no treatments available specifically for tumours with BRAF V600E mutations.

- Metastatic colorectal cancer treatment can involve a combination of:
    - surgery to resect the primary tumour or the metastases
    - chemotherapy to make the tumour or metastases resectable, or to manage the cancer

- o biological therapy
- o radiotherapy

1.2 The treatment pathway

Figure 1: treatment pathway for metastatic colorectal cancer



FOLFIRI	Fluorouricil/ leucovorin/ irinotecan
FOLFOX	Folinic acid/ 5-flurouricil/ oxaliplatin

*For EGFR-expressing, RAS wild-type

1.3 The technology

Marketing authorisation	Encorafenib is indicated in combination with cetuximab, for adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy.
Mechanism of action	Encorafenib: • Rapidly accelerated fibrosarcoma (RAF) kinase inhibitor. • Blocks the MAPK cell signalling pathway in BRAF V600E mutation-positive tumours. Cetuximab: • Recombinant monoclonal antibody that blocks the human epidermal growth factor receptor (EGFR).

	In combination: • Combining a RAF inhibitor with an EGFR inhibitor promotes anti-tumour efficacy by preventing activation of feedback loop that BRAF inhibition alone would otherwise activate.
Administration and dose	**Encorafenib** • Oral. 300 mg (four 75 mg capsules) once daily. Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity. **Cetuximab** • Summary of product characteristics: administered intravenously with infusion pump, gravity drip or syringe pump. Once a week, initial dose is 400 mg/m^2 body surface area, all subsequent doses are 250 mg/m^2. • Cetuximab is on the National Cancer Drugs Fund list, for the treatment of previously untreated metastatic colorectal cancer, it recommends that cetuximab is given once every 2 weeks at a dose of 500mg/m^2.
Additional tests or investigations	BRAF mutation testing: colorectal cancer with BRAF V600E mutation must be confirmed by a validated test, it should not be used in patients with wild type BRAF colorectal cancer.
Cost	**Encorafenib:** • List price £1,400 per pack of 42 x 75 mg capsules. • List price £622.22 per pack of 28 x 50 mg capsules. **Cetuximab:** • List price £890.50 per 500 mg/100 mL. *There are commercial arrangements in place for encorafenib and cetuximab, making the technologies available to the NHS with a discount. The size of the discount is commercial in confidence and is not reported here.*

1.4 The decision problem

	Final scope issued by NICE	**Company submission and ERG comments**
Population	People with previously treated BRAF V600E mutation-positive mCRC.	• Company: As per scope. • ERG: The population defined in the final scope could cover people who have received any number of prior therapies. The key trial included

		people who previously received either 1 or 2 regimen(s).
Intervention	Encorafenib with cetuximab, or Encorafenib with cetuximab and binimetinib	• Company: considers triple therapy no longer relevant to decision making. Company sought marketing authorisation only for dual therapy, encorafenib plus cetuximab.
Comparator	• Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Irinotecan • Trifluridine-tipiracil (only after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable) • Best supportive care	• Company: does not consider best supportive care a relevant comparator because it is positioned later in the treatment pathway when patients have exhausted all active treatment options. Does not consider single-agent irinotecan a relevant comparator because it is rarely used after 1st line in the NHS due to greater toxicity than combination treatment. • ERG: Notes that trifluridine-tipiracil may not be the most relevant comparator as it is used as a third- or subsequent-line therapy in clinical practice (see issue 2).
Outcomes	• Progression-free survival • Overall survival • Response rates • Adverse effects of treatment • Health-related quality of life	• ERG: Considers the outcomes in the company's submission match the outcomes described in the final NICE scope.

Professional organisation perspective (submission from Royal College of Physicians)

- BRAF mutant colorectal cancer is a very rare sub type of colorectal cancer.
- Despite advances in RAS wild type colorectal cancer we have seen very little shift in median survival for BRAF mutant cancer.
- FOLFIRI or alternatively trifluridine-tipiracil are currently used in clinical practice for this population. Encorafenib with cetuximab would be used in 2nd or 3rd line.
- No significant difference in adverse events expected compared with current treatments in NHS practice.

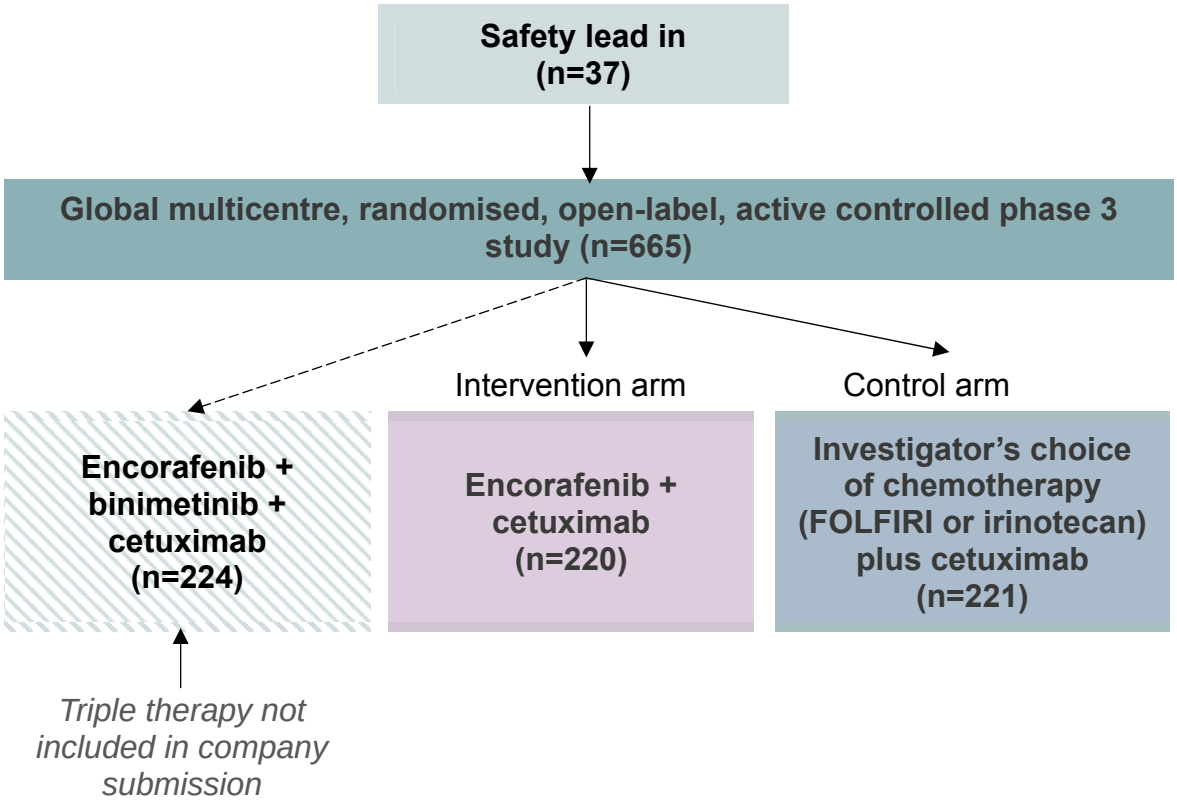
Encorafenib with cetuximab represents a 'step-change' in treatment. It is the only treatment to date that demonstrates both a clinically meaningful and statistically significant difference in terms of overall survival within this patient population in a phase 3 trial.

1.5 Clinical evidence

Trial design – BEACON CRC

BEACON CRC was designed specifically for patients with BRAF V600E-mutant metastatic colorectal cancer, whose disease had progressed after one or two prior regimens for metastatic cancer.

Figure 2: BEACON CRC trial design



NICE guidance restricts the use of cetuximab to first-line therapy in England (Figure 1). The choice of: FOLFIRI plus cetuximab, or irinotecan plus cetuximab, as the control arm of the BEACON CRC trial represented the most frequently used

therapeutic options globally among second- or third-line therapies at the time of study initiation. As a result:

- There are no head-to-head trials comparing encorafenib plus cetuximab with relevant comparators.
- The mapped evidence network of randomised controlled trials revealed a lack of common comparators and disconnected networks between the BEACON CRC trial and other trials.
- One randomised controlled trial (Peeters et al. 2010/2015) was identified for a potential indirect treatment comparison (ITC) for comparing encorafenib plus cetuximab with FOLFIRI.
- An ITC was not possible to compare encorafenib plus cetuximab versus trifluridine-tipiracil as no data were available for people with BRAF-mutant metastatic colorectal cancer.
- A naïve comparison using data from the RECOURSE study (Mayer 2015) was possible but included a population for whom BRAF status was not determined.

Additional clinical trial evidence

Table 1 Characteristics of clinical trials

Study title	BEACON CRC	Peeters et al. 2010/2015	RECOURSE (Mayer 2015)
Study design	Randomised controlled trial, phase 3	Randomised controlled trial, phase 3	Randomised controlled trial, phase 3
Population	People with BRAF V600E-mutant metastatic colorectal cancer ≤2 prior therapies	People with metastatic colorectal cancer treated with one prior chemotherapy *Subpopulation of BRAF-mutant metastatic colorectal cancer	People with metastatic colorectal cancer refractory or intolerant to standard therapies **~5% may have BRAF mutations >60% had ≥4 prior therapies
Intervention(s)	Encorafenib plus cetuximab	FOLFIRI plus panitumumab	Trifluridine-tipiracil

Study title	BEACON CRC	Peeters et al. 2010/2015	RECOURSE (Mayer 2015)
Comparator(s)	Investigator's choice of either irinotecan plus cetuximab, or FOLFIRI plus cetuximab	FOLFIRI	Best supportive care
Primary outcomes specified in the decision problem	Overall survival and overall response rate in the triple therapy arm	Progression free survival and overall survival	Overall survival
Secondary endpoints specified in the decision problem	Encorafenib plus cetuximab arm: overall survival, overall response rate, progression free survival, duration of response, health related quality of life	Overall response rate	Performance status, progression free survival
Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; FOLFIRI, folinic acid plus 5-fluorouracil plus irinotecan.			

Table 1. Comparison of selected baseline characteristics of participants in the BEACON CRC, Peeters et al 2010/2015 and RECOURSE trials

Baseline characteristics		BEACON CRC		Peeters et al 2010/2015		RECOURSE	
		IC (FOLFIRI or irinotecan) plus cetuximab (n=221)	**Encorafenib plus cetuximab (n=220)**	**FOLFIRI plus panitumumab (n=208)**	**FOLFIRI (n=213)**	**Trifluridine-tipiracil (n=534)**	Placebo (n=266)
				BRAF mutant sample size 10.7% n=45			
Age (years), median (range)		60 (27-91)	**61 (30-91)**	**60 (28-81)**	60 (33-85)	**63 (27-82)**	63 (27-82)
Female, N (%)		127 (58%)	**105 (48%)**	**72 (35%)**	73 (34%)	**208 (39%)**	101 (38%)
ECOG performance status	0	108 (49%)	**112 (51%)**	**196 (94%)**	198 (93%)	**301 (56%)**	147 (55%)
	1	113 (51%)	**104 (47%)**			**233 (44%)**	119 (45%)
	2	0 (0%)	**4 (2%)**	**NR**	NR	**0 (0%)**	0 (0%)

Number of prior regimens	1	145 (66%)	**146 (66%)**	**208 (100%)**	213 (100%)	**0 (0%)**	0 (0%)
	2	75 (34%)	**74 (34%)**	**0**	0	**95 (18%)**	45 (17%)
	3	1 (0.5%)	**0 (0%)**	**0**	0	**119 (22%)**	54 (20%)
	4	0 (0%)	**0 (0%)**	**0**	0	**320 (60%)**	167 (63%)
Prior anti -EGFR		0 (0%)	**0 (0%)**	**NR**	NR	**278 (52%)**	144 (54%)
Abbreviations: BRAF, B-Raf proto-oncogene; ECOG, Eastern Cooperative Oncology Group; NR, not reported							

1.6 Key trial results

BEACON CRC trial

Figure 1: progression free survival for encorafenib plus cetuximab vs control (source; company submission document B figure 4, p53)

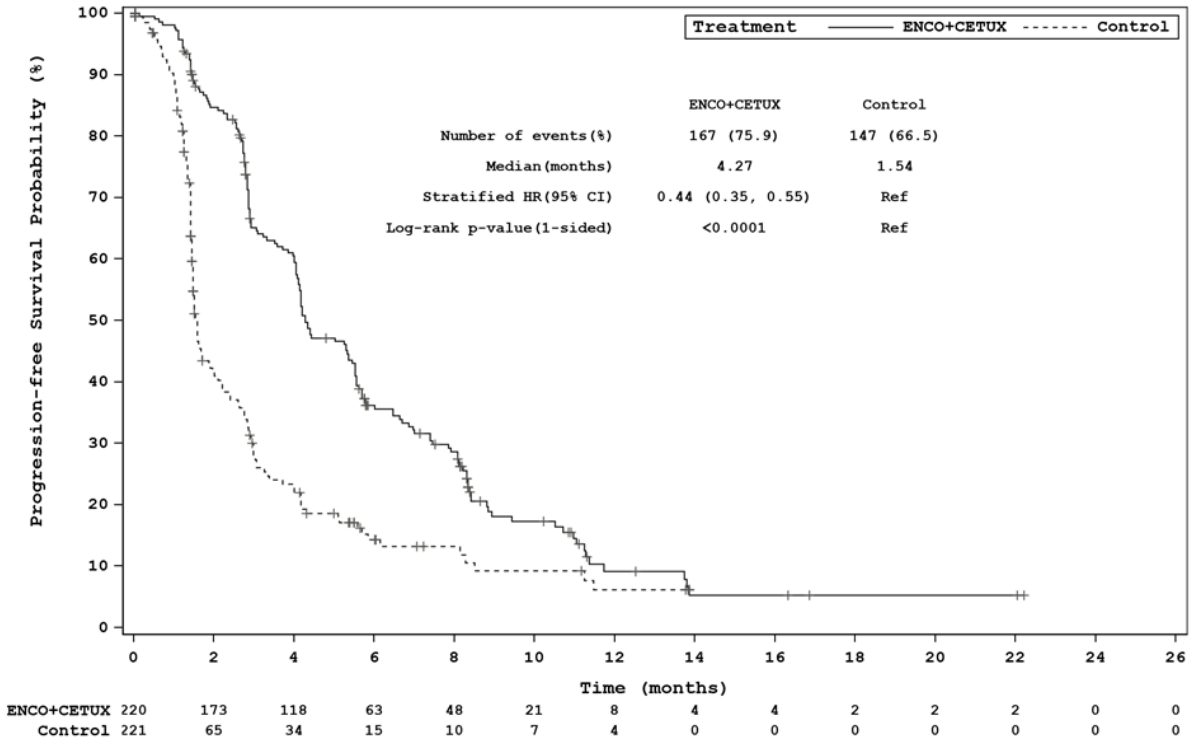
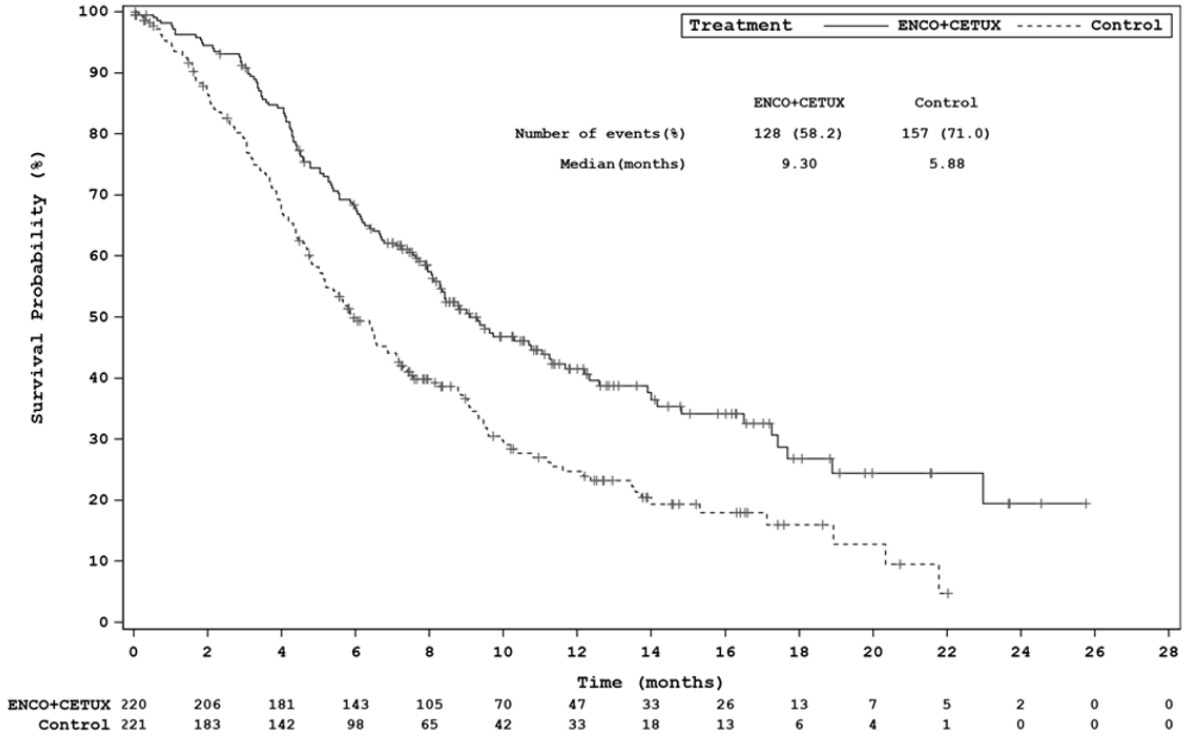


Figure 2: overall survival for encorafenib plus cetuximab vs control (source; company submission figure 3, p49)



Indirect treatment comparison

To estimate the relative efficacy of encorafenib plus cetuximab compared with FOLFIRI, the company performed an indirect treatment comparison (ITC) using data from the BEACON CRC trial and data from a subpopulation of BRAF positive patients in Peeters et al 2010/2015. There are no common comparators between these two studies. The ITC was only possible by applying several key assumptions:

- Equal efficacy of EGFR inhibitors, cetuximab and panitumumab (see issue 3)
- Equal efficacy of FOLFIRI plus cetuximab and irinotecan plus cetuximab (see issue 3)

(For more information see pages 58 to 68 of the company submission).

Figure 3: Indirect treatment comparison conducted in patients with BRAF V600E mutations

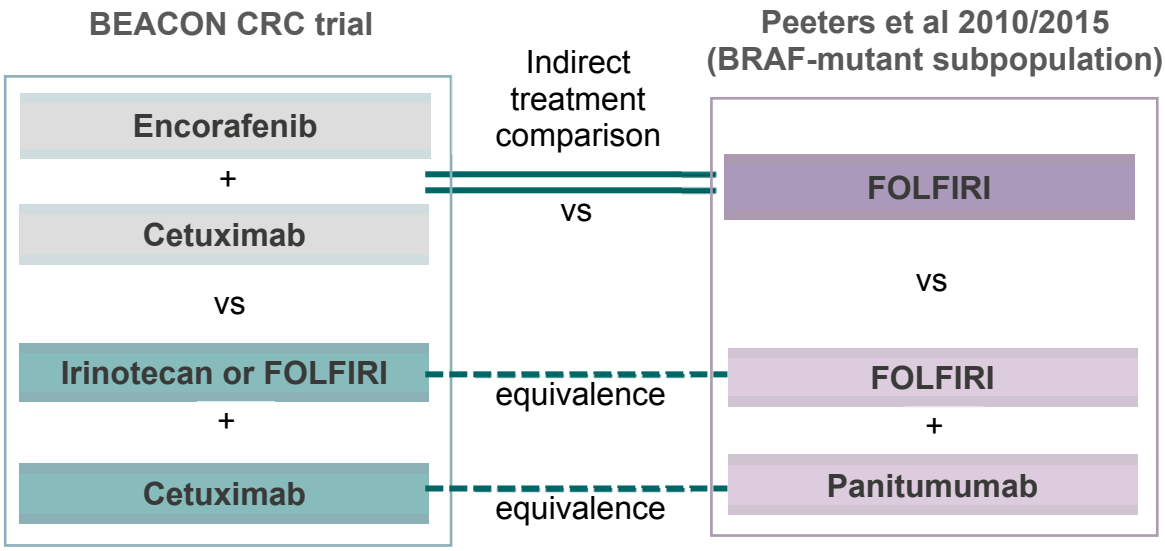


Table 3. Results from the company's Indirect Treatment Comparison (ITC) (Source: Table 8 ERG report)

Study	Overall survival (hazard ratio)	Progression free survival (hazard ratio)	
BEACON CRC trial	Encorafenib plus cetuximab vs. (FOLFIRI or irinotecan) plus cetuximab		
	0.61 (0.48, 0.77)	0.44 (0.35, 0.55)	Direct comparison
Peeters et al. 2010/2015	FOLFIRI plus panitumumab vs. FOLFIRI		
	0.64 (0.32, 1.28)	0.69 (0.32, 1.49)	Direct comparison
	Encorafenib plus cetuximab vs. FOLFIRI		
BEACON CRC trial Peeters et al. 2010/2015	0.39 (0.19, 0.81)	0.30 (0.14, 0.68)	Indirect comparison

Naïve comparison

Table 4. Survival results from the RECOURSE trial for the company's naïve comparison

Study	Treatment	OS	PFS
RECOURSE	Trifluridine-tipiracil	7.1 (6.5, 7.8)	2.0 (1.9, 2.1)
	Placebo	5.3 (4.6, 6.0)	1.7 (1.7, 1.8)

As the presence of the BRAF V600E mutation more than doubles the risk of mortality for people with metastatic colorectal cancer compared with wild-type metastatic colorectal cancer, the data used in the cost effectiveness model is adjusted for the poorer prognosis using data from the Peeters et al. 2010/2015 for BRAF-mutant and BRAF wild-type populations. Relative estimates of effect (hazard ratios [HR]) for OS 0.25 (0.18, 0.36) and PFS of 0.28 (0.20, 0.40), were calculated. The reciprocal (I/[HR]) was applied to the RECOURSE Kaplan-Meier data to provide estimates of effectiveness that may be more appropriate for the BRAF-mutant population.

1.7 Overview of how quality-adjusted life years accrue in the model

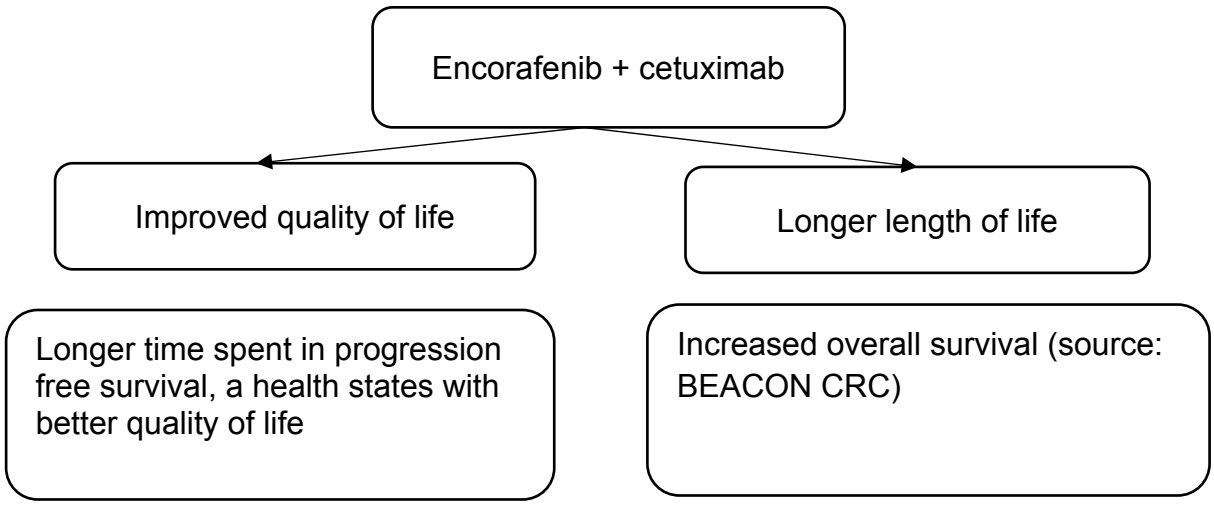
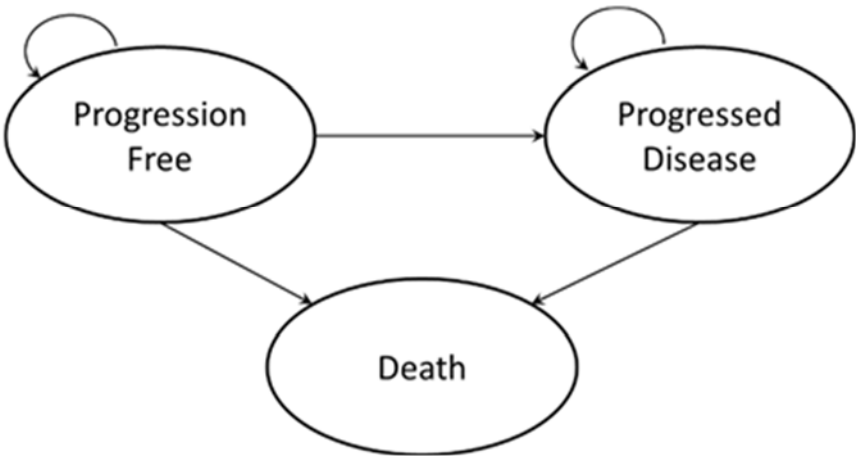


Table 2. Summary of utility values for cost-effectiveness analysis (Source: Table 43 company submission)

	Mean utility		
Treatment	Encorafenib plus cetuximab	FOLFIRI	Trifluridine-tipiracil
Source	BEACON CRC intervention arm	BEACON CRC control arm	Mean of encorafenib plus cetuximab and FOLFIRI utilities
Progression-free	0.743	0.741	0.742
Post-progression	0.622	0.631	0.627

1.8 Model structure



The company constructed a partitioned survival model with 3 health states (progression-free, progressed, and dead). The probability of being in each model state at time t is estimated for each health state as:

- *Progression Free Survival*: calculated using the progression free survival function (constrained by the overall survival function) at time t.
- *Post Progression Survival*: calculated as the difference between the cumulative survival probabilities at time t for OS and PFS.
- *Death*: This uses the OS survival function at time t.

In the company's base case, a model time horizon of 10 years was applied.

1.9 Key model assumptions

Table 6. Key model assumptions in the company's base case

Relative efficacy estimate for encorafenib plus cetuximab vs FOLFIRI	Estimated from company's indirect treatment comparison
Relative efficacy estimate for encorafenib plus cetuximab vs trifluridine-tipiracil	Estimates from a naïve comparison of BEACON CRC data and RESOURCE trial data adjusted by the application of BRAF-mutant versus wild-type hazard ratios.
Modelling overall survival + progression free survival	Curves were fitted to data to extrapolate overall survival and progression free survival. The loglogistic curve was deemed most appropriate based on AIC and visual inspection.
Duration of treatment	• Time to discontinuation is similar to progression free survival (see issue 6). Patients would be expected to remain on treatment whilst they were progression-free. • At progression, patients in the encorafenib plus cetuximab arm and in the FOLFIRI arm are assumed to receive an average of one month of treatment with trifluridine-tipiracil.
Treatment waning	No waning of treatment effect after the trial period.
Health related quality of life	• Heath related quality of life is based on treatment arm-specific EQ-5D derived from BEACON CRC trial. Estimates for FOLFIRI alone based on the control arm. • Company assumed utilities decline over the 10 year time horizon by the same proportion as the decline in the age/sex adjusted general population values. • Company assumed quality of life values for trifluridine-tipiracil are the average of encorafenib plus cetuximab and the comparator arm.
Adverse events	• Company estimated cost of adverse events for encorafenib plus cetuximab were estimated from the BEACON CRC trial data, FOLFIRI from RAISE clinical trial (FOLFIRI alone in patients with mCRC) and trifluridine-tipiracil using data from the RECOURSE study. Company did not include disutilities for adverse events in its model.
Health state costs	Company assumed post progression health state costs are the same for encorafenib plus cetuximab and FOLFIRI.

Treatment costs	Vial sharing between patients is assumed for intravenous therapy and there is no wastage.
More details on key assumptions in the company's model in the ERG report, pages 80 to 102.	

2. Summary of the technical report

2.1 In summary, the technical team considered the following:

Issue 1 The company have positioned encorafenib plus cetuximab as a 2nd or 3rd line treatment for people with mCRC with a BRAF-V600E mutation. Relevant comparators are FOLFIRI or trifluridine-tipiracil. The technical team welcomes comments on when encorafenib plus cetuximab would be used instead of trifluridine-tipiracil.

Issue 2 If trifluridine-tipiracil is an appropriate comparator, the naïve comparison between encorafenib plus cetuximab and trifluridine-tipiracil in the specific BRAF mutant patient population is highly uncertain.

Issue 3 Including cetuximab in both the intervention and control arms in the BEACON CRC trial and paucity of data for the population with BRAF mutations requires company to make clinical assumptions for an indirect treatment comparison. Several clinical assumptions are highly uncertain.

Issue 4 Efficacy of cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer is uncertain.

Issue 5 There are issues with fitting parametric models to the trial data. Modelling overall survival affects the estimated clinical and cost-effectiveness results. The company should use appropriate data, and apply a suitable extrapolation method.

Issue 6 There are issues with fitting parametric models to the progression free survival data. The technical team welcomes

comments on using raw Kaplan-Meier data to model progression free survival.

Issue 7 The company's model assumes that time to treatment discontinuation is the same as progression free survival. The time to discontinuation curves differ from the progression free survival curves from month 5 onwards. Further analyses are requested to test the sensitivity of the model to this assumption.

Issue 8 Health utility values are treatment specific. There are potential validity issues with post-progression values.

Issue 9 Drug acquisition and administration costs may be underestimated for encorafenib plus cetuximab and correcting this would likely increase the ICER for encorafenib plus cetuximab. Other cost uncertainties surrounding drug wastage and relative dosing intensities may impact the ICER estimates.

Issue 10 Treatment of previously-treated BRAF V600E mutation-positive metastatic colorectal cancer may meet NICE's end of life criteria, but some uncertainties remain.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- There is no evidence directly comparing encorafenib plus cetuximab with relevant comparators.
- There is limited evidence available for the population of interest, that is people with previously treated BRAF V600E mutation-positive colorectal cancer.

2.3 The cost-effectiveness estimates in this report are based on list prices. There are confidential discounts (commercial arrangements) for encorafenib, cetuximab and trifluridine-tipiracil. The cost-effectiveness results taking the commercial arrangements into account are confidential and are not reported here.

2.4 Using list prices, the ERG's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of £242,000 per QALY gained (rounded to 3 significant figures; see table 1). This estimate does not include the commercial arrangements for encorafenib, cetuximab and trifluridine-tipiracil. Estimates that include these commercial arrangements would be lower than those reported above.

2.5 Based on the modelling assumptions, the intervention is likely to meet the end-of-life criteria (see issue 9).

2.6 The company place encorafenib plus cetuximab as an innovative treatment that represents a step change in clinical practice. Clinical experts agree that there is an unmet need, as there is currently an absence of treatments specifically for patients with colorectal tumours with BRAF V600E mutations. A treatment for this population that is well tolerated would be welcomed by patients and clinicians.

2.7 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Treatment pathway

Questions for engagement	1. Where would encorafenib plus cetuximab likely be used in NHS clinical practice? Is 2nd line the only relevant position for the committee to consider in its decision making? 2. Is single agent irinotecan an established 2nd line treatment for people with BRAF V600E mutation-positive metastatic colorectal cancer? 3. Is best supportive care a relevant comparator for people with previously treated BRAF V600E mutation-positive metastatic colorectal cancer? 4. Where in the treatment pathway is trifluridine-tipiracil used? Is trifluridine-tipiracil a relevant comparator for encorafenib plus cetuximab?
Background/description of issue	Encorafenib plus cetuximab has a positive CHMP opinion for treating people with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy. The **company** excludes single agent irinotecan as a relevant comparator because according to expert opinion and a market survey it is rarely used as a second line treatment option. The company found less than 2% of patients receive single agent irinotecan in clinical practice. The company excludes best supportive care as a comparator because encorafenib plus cetuximab would be used earlier in the treatment pathway, where active treatments are still available. The **ERG** agrees with the company that it is appropriate to exclude single agent irinotecan and best supportive care as comparators. The **company** includes trifluridine-tipiracil as a relevant comparator as it has been appraised through NICE's TA process (TA405) and is the only regimen recommended after first-line therapy in the NICE Pathway. The **technical team** notes that the marketing authorisation for trifluridine–tipiracil allows for its use in 2nd line, although in TA405 the "committee agreed that, in clinical

	practice, trifluridine–tipiracil would mainly be used in people who have previously had 2 or more therapies when there are no further treatment options". The **ERG** notes trifluridine-tipiracil is used in current clinical practice as a third or subsequent line treatment option. The ERG considers encorafenib plus cetuximab is most likely to be used as an alternative option to FOLFIRI as a second line therapy. The **clinical experts** noted their preference for using encorafenib plus cetuximab at second line. They considered the most relevant comparator for this appraisal to be FOLFIRI but suggested some patients who received FOLFOXIRI at first line would receive trifluridine-tipiracil at second line. For this small group of patients trifluridine-tipiracil would be a relevant comparator.
Why this issue is important	To appraise encorafenib plus cetuximab for use within the NHS, the committee must understand the position in the treatment pathway. Determination of clinical practice relates to several of the key issues outlined in this report. For example, whether the studies in the ERG and the company's economic analysis are generalisable to clinical practice.
Technical team preliminary judgement and rationale	The technical team agree with the ERG and company that single agent irinotecan and best supportive care are not relevant comparators. Further clinical expert advice is sought on when encorafenib with cetuximab would be used instead of trifluridine-tipiracil.

Issue 2 – Relevant comparators

Questions for engagement	5. Does having a larger proportion of refractory patients in the RECOURSE trial have an impact on survival outcomes when compared to the BEACON CRC trial? 6. Are outcomes of patients who have previously received EGRF inhibitors expected to differ from patients who are EGRF naïve? Does this differ by place in the treatment pathway? 7. Are the RECOURSE data used in the economic modelling robust and appropriate for decision making?

Background/description of issue	There is no evidence directly, or indirectly comparing encorafenib plus cetuximab with trifluridine-tipiracil for patients with metastatic colorectal cancer with BRAF V600E mutations. The **company** presented a naïve comparison using data from the intervention arm of the RECOURSE trial for a population of patients for whom BRAF status was not defined. The company adjusted the effectiveness outcomes from RECOURSE by the relative effect seen in BRAF-mutant and BRAF wild-type populations for overall survival and progression free survival. Hazard ratios from the Peeters 2010/15 trial were used to estimate survival for patients with BRAF mutations treated with trifluridine-tipiracil. The company acknowledge the issues of uncertainty introduced when performing a naïve comparison, but highlight the paucity of data available in the specific population of interest The **ERG** state that the generalisability of the RECOURSE trial to the population of interest is limited as; • 60% had 4 or more prior therapies vs only 1 prior systemic therapy for 66% of patients in the BEACON CRC trial • The BEACON CRC trial excluded patients with prior EGFR use, but more than half of patients in the RECOURSE trial had been treated with an anti-EGFR at baseline The ERG note that the substantial differences in treatment history between the patient populations may bias the naïve comparison in favour of encorafenib plus cetuximab. It is the ERGs opinion that there is insufficient data to support a reliable comparison of encorafenib plus cetuximab with trifluridine-tipiracil. The effectiveness of trifluridine-tipiracil has not been evaluated in the population with BRAF V600E mutant metastatic colorectal cancer, therefore the ERG have not included it in the economic analysis. The **NICE technical team** note that the hazard ratio applied by the company as part of the naïve comparison is assumed to be the same for all treatments but there is no evidence presented to support this assumption.

Why this issue is important	There is uncertainty about whether the clinical evidence is reflective of the populations of interest and, when used in the economic modelling, whether it is robust and appropriate for decision making. This introduces uncertainty in whether encorafenib plus cetuximab is a cost-effective option in people who would have received trifluridine-tipiracil therapy.
Technical team preliminary judgement and rationale	The technical team agree with the ERG that a comparison of encorafenib plus cetuximab versus trifluridine-tipiracil is highly uncertain. The lack of comparative data makes the assessment of comparative effectiveness (and any cost-effectiveness analyses) challenging. Further evidence is sought on the appropriateness of applying a hazard ratio from different treatment regimens to account for the poorer prognosis in survival outcomes between BRAF and wild-type metatastatic colorectal cancer.

Issue 3 – Indirect treatment comparison

Questions for engagement	8. How does FOLFIRI compare to irinotecan in terms of clinical effectiveness? Would efficacy of either treatment be different in the BRAF-mutant population compared to wildtype? 9. How does cetuximab compare to panitumumab in terms of clinical effectiveness?
Background/description of issue	BEACON CRC was a multinational, open-label, randomised, phase III trial comparing encorafenib in combination with cetuximab versus investigator's choice of chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab. The use of EGFR inhibitors for metastatic colorectal cancer is not recommended in UK clinical practice beyond first line treatment. To indirectly compare encorafenib encorafenib in combination with cetuximab to FOLFIRI the **company** compared the control arm in the BEACON CRC study (FOLFIRI or irinotecan, plus cetuximab) with outcomes from a subpopulation of BRAF-mutant positive patients who received FOLFIRI plus panitumumab in the Peeters et al. 2010/2015 study in an indirect treatment comparison (ITC). The ITC was only possible by applying two key assumptions: • Equivalence of EGFR inhibitors – cetuximab and panitumumab

	• Equivalence of FOLFIRI plus cetuximab and irinotecan plus cetuximab The **company** justified these assumptions: • *Cetuximab and panitumumab:* a class effect is assumed as the drugs are both EGFR inhibitors. The company sought clinical expert opinion and highlight the committee conclusion in NICE TA439 cetuximab and pnitumumab for previously untreated metastatic colorectal cancer, 'cetuximab and panitumumab were likely to have similar effectiveness in treating RAS wild-type metastatic colorectal cancer'. • *FOLFIRI and irinotecan:* results from clinical trials comparing irinotecan with FOLFIRI are presented, showing there is no statistically significant difference in progression free survival and/or overall survival between treatment arms (Clarke et al., 2011 and Graeven et al., 2007). Baseline charcteristics are presented in section **Error! Reference source not found.** of the technical report and the results of the indirect treatment comparison are presented in section **Error! Reference source not found.** of the technical report. The **ERG** was concerned that the two assumptions made by the company were not fully supported by the wider evidence: • *Cetuximab and panitumumab:* Evidence of a class effect is limited to wildtype RAS metastatic colorectal cancer and may not be generalisable to previously treated BRAF V600E mutation-positive metastatic colorectal cancer (see issue 4) • *FOLFIRI and irinotecan:* o The trials identified by the company do not specifically include the BRAF mutant population. o Evidence from the BEACON CRC control arm split by whether the patients received FOLFIRI plus cetuximab or irinotecan plus cetuximab showed [redacted] plus cetuximab. The ERG acknowledges the trial was not sufficiently powered for

	comparisons between the two control options, that treatment was not randomised and note the company data suggesting substantial differences between patients receiving FOLFIRI plus cetuximab or irinotecan plus cetuximab in the control arm. The **clinical experts** noted limited data was available in this population. However, they considered the efficacy of FOLFIRI and irinotecan to be equal in both the wildtype and BRAF-mutant populations. They noted that there were differences in toxicity profiles which may affect outcomes for patients receiving irinotecan in clinical practice. They also considered the efficacy of cetuximab and panitumumab to be equal noting that they were used interchangeably in clinical practice when it was permitted to use EGRF inhibitors in this population.
Why this issue is important	The company may have introduced biased by assuming in its indirect treatment comparison that the estimates of relative effectiveness are equal. Using alternative data to estimate relative effectiveness (for example directly from the BEACON CRC trial), has a large impact on the ICER.
Technical team preliminary judgement and rationale	The assumptions of the company's indirect treatment comparison are reasonable but uncertain. Scenarios exploring relative effectiveness from alternative sources are useful to determine the effect on the ICER.

Issue 4 – BEACON CRC trial as a proxy for estimating relative effectiveness

Questions for engagement	10. Is cetuximab clinically effective for people with previously treated BRAF V600E mutation-positive metastatic colorectal cancer?
Background/description of issue	**The company** acknowledge limitations and required assumptions of the indirect treatment comparison (see issue 3 and section 1.6). They note the indirect treatment comparison allowed evidence for FOLFIRI, when administered alone, to be indirectly compared with the encorafenib plus cetuximab and generate an estimate of effectiveness. The **ERG** notes the evidence does not support an underlying assumption made by the company in the indirect treatment comparison that cetuximab is clinically effective for people with previously treated BRAF V600E mutation-positive metastatic colorectal cancer. The ERG presents the following critique of the company's assumption.

- The estimated hazard ratios from the Peeters 2010/2015 trial for panitumumab plus FOLFIRI vs. FOLFIRI were not statistically significant
- 2 systematic reviews looking at the effectiveness of anti-EGFRs in people with BRAF mutant metastatic colorectal cancer showed no statistically significant benefit for anti-EGFRs in a BRAF mutant metastatic colorectal cancer population.
- The ERG conducted an alternative indirect treatment comparison using data from the PICCOLO study. The ERG's alternative indirect treatment comparison requires the same assumptions as the company indirect treatment comparison but compares encorafenib plus cetuximab with single agent irinotecan. The results of the ERG's alternative indirect treatment comparison suggested no significant difference between encorafenib plus cetuximab and irinotecan, with overall survival in favour of irinotecan and progression free survival in favour of encorafenib plus cetuximab.

Table 7. Results from the ERGs indirect treatment comparison (source ERG report table 10, p55)

Study	Overall survival (Hazard Ratio)	Progression free survival (Hazard Ratio)	Comparison
BEACON CRC	Encorafenib plus cetuximab vs. (FOLFIRI or irinotecan) plus cetuximab		
	0.61 (0.48, 0.77)	0.44 (0.35, 0.55)	Direct comparison
PICCOLO	Irinotecan (n=31) plus Panitumumab vs. irinotecan (n=37)		
	1.84 (1.10, 3.08)	1.40 (0.82, 2.39)	Direct comparison
	Encorafenib plus cetuximab vs. irinotecan		

	Indirect treatment comparison	1.12 (0.64, 1.98)	0.62 (0.34, 1.10)	Indirect comparison

The ERG notes that these findings should be treated with great caution. There are substantial differences in patient population between the PICCOLO and BEACON CRC trials, and only a small number of patients had BRAF mutations in PICCOLO.

The ERG highlight the substantial uncertainties associated with assumptions required for both ITCs and the little benefit of anti-EGFRs in the BRAF-mutant population.

The ERG considers the company's indirect treatment comparison to be biased in favour of encorafenib plus cetuximab as it overestimates the effect of cetuximab.

Given the importance of the assumptions made by the company and the limitations of its indirect treatment comparison, the ERG concludes that the company's estimates are highly uncertain and not reliable to form the basis of cost-effectiveness analysis. The ERG considers the randomised comparison between the encorafenib plus cetuximab arm and the control arm of the BEACON CRC trial as the most suitable proxy for estimating the relative effectiveness of the technology compared with FOLFIRI.

The **clinical experts** explained people with previously treated BRAF V600E mutation-positive metastatic colorectal cancer were likely to get short term response from cetuximab, but the benefit was limited as it activated resistance pathways. They were uncertain whether outcomes from the BEACON CRC control arm would be comparable to current clinical practice with FOLFIRI. They noted patients treated with EGRF inhibitors in later lines (3rd and subsequent) may have short responses to treatment and survival benefit, but this was not approved for use in the NHS in England and no evidence is available.

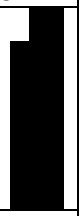
Why this issue is important	There is no direct comparative data for encorafenib plus cetuximab vs FOLFIRI. The only available data may not be sufficiently robust to determine the differences between the technologies in how well they work. Using alternative proxy data to estimate relative effectiveness of encorafenib plus cetuximab (for example directly from the BEACON CRC trial), has a large impact on the ICER.

Technical team preliminary judgement and rationale	It is unclear whether there is any additional benefit from cetuximab in people with BRAF-mutations. The technical team note that there is disparity between clinical evidence and expert advice. The technical team would welcome further input about the expected differences between the BEACON CRC trial and clinical practice to determine which data source(s) are appropriate for decision making.

Issue 5a – Modelling overall survival for BEACON CRC encorafenib plus cetuximab data

Questions for engagement	11. For people who have had previous treatment for metastatic BRAF-V600E mutation positive colorectal cancer, and received encorafenib plus cetuximab, what proportion would you expect to survive to 3 years and to 5 years? 12. How informative is the ERG's analysis regarding the extrapolation of overall survival?
Background/description of issue	The **company** fitted a range of curves, to the BEACON CRC encorafenib plus cetuximab arm using individual patient level data to estimate overall survival. Visual inspection of the curves showed that the proportional hazards assumption had not been violated for overall survival.The company selected the log-logistic model from statistical goodness-of-fit (AIC and BIC across all treatment arms) and visual comparison. The company consulted clinical experts who agreed the log-logistic model produced clinically valid results. At 5 years 4% of people were alive having received encorafenib plus cetuximab. The clinical experts also noted that the Weibull model gave plausible estimates of long-term survival, although some believed these may be conservative with almost all patients having died at 5 years (>99%). The company provided this model in a scenario analysis. The **ERG** accepts the log-logistic as a plausible extrapolation and agreed that it was the best statistical fit according to AIC and BIC. However, the ERG note that all the curves fitted poorly to the trial data.

	The ERG considers the shape of the Kaplan-Meier curve makes it difficult for any of the parameterised curves to fit precisely. The ERG examined the cumulative hazard plot and found a clear change of trajectory of the hazard rate at 2.8 months. The ERG fit models only to data occurring beyond 2.8 months. The model applies the KM data for the first three cycles. The fitted curves are then applied, reduced prorate by the 3 month KM S(t) proportion. The ERG selected the exponential model based on AIC, BIC and clinical plausibility, ruling out curves that predicted a substantial proportion surviving 10 years or more. **Table 8. Overall survival predictions for encorafenib plus cetuximab based on ERG and company extrapolations (Source: ERG report, p82, table 84)**

Model		Percentage alive at: (time and the percentage of patients are modelled both from original time = 0)		
		3 years	5 years	10 years
ERG	Gompertz Generalised gamma **Exponential** Weibull Log-normal Log-logistic			
Company base case	Log-logisitc			

Why this issue is important	The choice of extrapolation method to model survival affects the estimated clinical and cost-effectiveness results. It is important that the data are appropriate and any method used is valid. Amending the modelling assumptions has the potential to substantially change the ICER estimates.
Technical team preliminary judgement and rationale	The technical team considers that the company's choice of model to extrapolate overall survival for the intervention arm may be reasonable, but the use of other potentially valid models should be explored to capture uncertainties associated with the choice of model. Further analyses using a

	complete piecewise approach and exploring if fitting an extrapolated model to alternative timepoints on the KM curve effects the long term projections are requested from the company.

Issue 5b – Modelling overall survival for the comparator arm

Questions for engagement	13. For people who have had previous treatment for metastatic BRAF-V600E mutation positive colorectal cancer, and receive current standard of care as 2nd line what proportion would you expect to survive to 3 and 5 years respectively? 14. Based on data presented is the company's approach to modelling overall survival appropriate?
Background/description of issue	The **company** fitted parameterised curves to the BEACON CRC encorafenib plus cetuximab arm and applied the hazard ratio (2.56 [95% CI 1.23 – 5.26]) from the indirect treatment comparison to the encorafenib plus cetuximab OS survival curve to estimate the control arm and generate survival curves for FOLFIRI. The company selected best-fitting parametric model across all treatments, choosing the log-logistic model. Clinical experts agreed it produced clinically valid results for the comparator arm; with 2.4% of people alive at 5 years. The company note that the control arm cannot be used to estimate the relative effectiveness between encorafenib plus cetuximab and FOLFIRI alone because cetuximab is also used in the control arm. However, clinical opinion suggests any benefit of cetuximab would be limited so the company provide scenario analyses using the BEACON CRC control arm as the comparator. The **ERG** states that the company's approach to modelling overall survival results in estimates that vary considerably from the observed data for the control arm in the BEACON CRC trial (Figure 4). **Figure 4: deviation of company modelling of overall survival from the BEACON CRC trial control arm (source ERG report p79, figure 17)**

[redacted]

The ERG prefers to model overall survival for FOLFIRI by fitting parameterised curves to the Kaplan Meier data from the control arm of the BEACON CRC trial. The ERG modelled both arms of the BEACON CRC trial simultaneously using 2.8 months as time 0 (see Issue 5a).

Table 9. Overall survival predictions for comparator arm based on ERG and company extrapolations (Source: ERG report, p82, table 84)

Model		Percentage alive at: (time and the percentage of patients are modelled both from original time = 0)		
		3 years	5 years	10 years
ERG	Gompertz Generalised gamma Exponential Weibull Log-normal Log-logistic	[redacted]	[redacted]	[redacted]

	Company base case	Log-logisitc	[redacted]	[redacted]	[redacted]	
Why this issue is important	The choice of data used to model survival affects the estimated clinical and cost-effectiveness results. It is therefore important that the data are appropriate and any extrapolation method used is valid. Amending the modelling assumptions has the potential to substantially change the ICER estimates.					
Technical team preliminary judgement and rationale	The technical team considers that the company's choice of model to extrapolate overall survival, applying the hazard ratio from the indirect treatment comparison for the intervention arm is useful. However, the use of other potentially valid models should be explored to capture uncertainties associated with the choice of model.					

Issue 6 – Modelling progression free survival

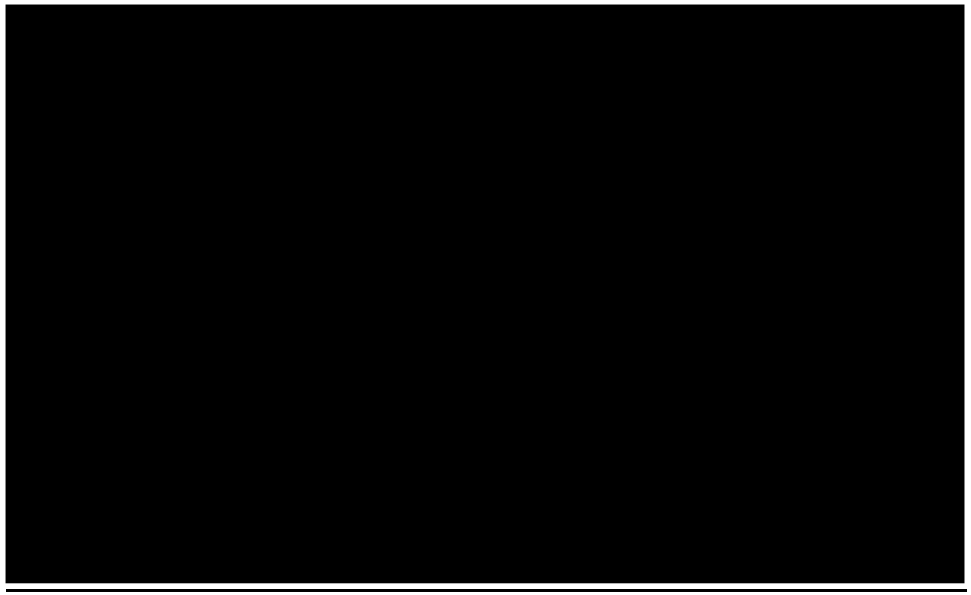
Questions for engagement	15. What proportion of patients would be expected to remain progression free at 3 years after having had encorafenib plus cetuximab? 16. Is the ERG's approach to modelling progression free survival appropriate?
Background/description of issue	The **company** used the same approach to modelling progression free survival as for overall survival (issue 5a and b), fitting individual parametric models to the intervention arm using the log-logistic model and extrapolating beyond the observed period of the trial. To estimate PFS for FOLFIRI, the company applied the hazard ratio obtained from the ITC. The **ERG** notes that the company's approach to modelling progression free survival results in at least 1% of patients on encorafenib plus cetuximab remaining in the progression free health state for up to 3.4 years, considerably longer than the current follow-up of the trial. The company's approach also estimates that less than 1% of patients are progression free on FOLFIRI at 9 months. Further, because the proportional hazards assumption is violated it is not appropriate to apply hazard ratios from the independent treatment comparison to the PFS curve.

	The ERG found that none of the parametric curves fit the Kaplan-Meier data well and noted that the cumulative hazard plot was unusually shaped. The ERG applied the observed progression free survival data from the BEACON CRC trial without using a parametric curve. The ERG's approach artificially curtails the progression free survival curves but the ERG does not consider this a major issue. The ERG also provided a number of scenario analyses which explored fitting parameterised curves to the progression free survival data in a similar approach to that used for overall survival but using a cut-off point of 1.8 months.
Why this issue is important	The approach to modelling progression free survival has a moderate impact on the ICER. Using the ERG's approach of applying the BEACON CRC Kaplan-Meier data to model progression free survival decreases the company's base case ICER.
Technical team preliminary judgement and rationale	Given that none of the parametric models offers a good fit to the data on progression free survival, the technical team prefers to apply the Kaplan-Meier data from BEACON CRC directly to model progression free survival. However, the technical team requests that the company perform further analyses using a piecewise approach to modelling PFS.

Issue 7 – Modelling time to treatment discontinuation

Questions for engagement	17. Is it appropriate to assume that time to treatment discontinuation is the same as progression free survival for encorafenib plus cetuximab and the relevant comparators?
Background/description of issue	The company assumed that time to treatment discontinuation was equivalent to progression free survival. This assumption was supported by clinical experts who agreed it reflected current clinical practice. The company presented the BEACON CRC Kaplan-Meier time to treatment discontinuation (TTD) plots alongside the KM PFS plots for encorafenib plus cetuximab and the BEACON CRC control arm. The company note the 95% confidence intervals overlap and p values indicate the time to discontinuation and progression free survival curves are not statistically different (p=0.46 encorafenib plus cetuximab and p=0.19 comparator) (see figure 5 and figure 6).

	Figure 5: time to discontinuation and progression free survival Kaplan-Meier curves for the encorafenib plus cetuximab arm 

	Figure 6: time to discontinuation and progression free survival Kaplan-Meier curves for the BEACON CRC control arm  The ERG does not think it's appropriate to conclude that time to treatment discontinuation is the same as progression free survival. It notes that in both the treatment and control arm the PFS curve differs from the TTD curve after month 5: • In the encorafenib plus cetuximab arm, a higher proportion of patients remain on treatment than are progression free • In the control arm, a higher proportion of patients are progression free than remain on treatment. Further, the PFS curve treats some events as missing data, whereas the TTD curve treats them as discontinuation events, including withdrawal of consent and receiving subsequent treatment.

Why this issue is important	The time to discontinuation curves show that people having encorafenib plus cetuximab remain on treatment for slightly longer than progression free survival and people in the control arm appear to discontinue treatment before disease progression. This could lead to the cost-effectiveness results being biased in favour of encorafenib with cetuximab.
Technical team preliminary judgement and rationale	Treatment beyond progression is not included in the company's model but time to treatment discontinuation curves show some patients may have continued to receive treatment after progression. The technical team requests that the company provide a scenario analysis where time to discontinuation is used in the model.

Issue 8 – Utility values

Questions for engagement	18. Are the utility values included in the company model appropriate?
Background/description of issue	Health related quality of life was assessed using the EQ-5D-5L health state utility index (mapped to EQ-5D-3L values). The **company** applied health state utilities by progression status for both the intervention and control arm. For encorafenib plus cetuximab mean EQ-5D values were taken from the encorafenib plus cetuximab arm, results from the BEACON CRC control arm (FOLFIRI or irinotecan, plus cetuximab) were used to estimate utility for FOLFIRI. To estimate the utility of patients on trifluridine-tipiracil, the mean of the encorafenib plus cetuximab and the control arm utilities was taken for each health state. As the utility data came directly from the treatment arms of the BEACON CRC trial, the company did not apply additional adverse event disutilities. The company noted clinical expert feedback indicated that the primary driver of HRQoL in mCRC patients is their progression status and not the treatment they take. The **ERG** notes that the mean post progression state (PPS) EQ-5D data used by the company extends only to 30 days post progression follow-up, and the estimated time in the PPS state in the company model is 9.4 months. The ERG suggest that it is possible that quality of life in PPS declines over time. The ERG notes that the values of quality of life values for post progression survival for FOLFIRI plus cetuximab are better than those for irinotecan plus cetuximab. As irinotecan can be poorly tolerated and is not a relevant comparator for this appraisal, the ERG applies the higher utility values for the post progression survival state of the comparator arm.

Why this issue is important	The approach to modelling quality of life during the post progression state has a moderate impact on the ICER, using the ERG's approach moderately increases the company's base case ICER.
Technical team preliminary judgement and rationale	The technical team notes clinical expert advice that single-agent irinotecan is poorly tolerated and not used in clinical practice. The technical team therefore agrees with the ERG's approach of applying utilities specific to FOLFIRI from the comparator arm of the BEACON CRC trial.

Issue 9 – Cost uncertainties in the analysis

Questions for engagement	19. What is the correct dosage of cetuximab in clinical practice? 20. Do differences in the dose of cetuximab impact on the cost-effectiveness estimates? 21. Is the assumption of no drug wastage reasonable?
Background/description of issue	There are a number of uncertainties in the analysis associated with costs and resource use: 1. There were differences in the dosage for cetuximab. The **ERG** notes that the 1st cycle cost of cetuximab differs from subsequent cycles due to a loading dose. The ERG thinks that the SmPC specifies a 7-day loading dose, after which ongoing cetuximab dosing is applied. The **company** costs the 1st cycle as the loading dose plus half the ongoing monthly cost. 2. The **company** applies relative dose intensity (RDI) percentages to account for actual doses received during the trials compared to the planned dosing. The **ERG** highlights that the relative dose intensity data from the BEACON CRC trial is skewed, with the median RDI considerably higher than the mean. This is likely a result of 'some patients faring poorly in the early period of the trial' noting that those who remain in the trial have a better relative dose intensity. Applying the mean relative dose intensity would underestimate cetuximab use. The ERG applies median relative dose intensities for cetuximab.

	3. The **company** assumes that vials can be shared between patients and that there is no waste. This mainly reduces the cetuximab costs in the encorafenib plus cetuximab arm. ERG expert opinion suggests that vials are shared between patients when possible, but that there is still wastage due to this being less than perfect.
Why this issue is important	To have confidence in reported cost-effectiveness results, analysis should attempt to capture the likely costs that would be incurred in NHS clinical practice for each potential treatment option.
Technical team preliminary judgement and rationale	The ERG's scenario analysis is useful as it attempts to account for some areas of cost uncertainty within the analyses. The potential underestimation of drugs costs due to the dosing schedule for cetuximab should be investigated and amended by the company to provide more accurate cost-effectiveness estimates. The technical team believes that assuming zero drug wastage to be an unlikely scenario and requests a scenario analysis exploring alternative assumptions on drug wastage.

Issue 10 – End of life criteria

Questions for engagement	22. Does the evidence support that encorafenib plus cetuximab extends life by a mean of 3 months or more compared with current practice? 23. Under standard care, is the life expectancy of adults with previously treated BRAF-V600E mutation positive metastatic colorectal cancer have a mean of less than 24 months?
Background/description of issue	The **company** believes that encorafenib plus cetuximab for the treatment of patients with BRAF V600E-mutant metastatic colorectal cancer who have received prior systemic therapy meets NICE end-of-life criteria. They note life expectancy estimate with standard of care is around 4–6 months but there is limited evidence in the specific population of interest. The BEACON CRC trial reported a **median** overall survival 5.88 months (95% CI 5.09 to 7.10) for the comparator arm.

	The **company's** model estimates a mean overall survival difference of 10.1 months for encorafenib plus cetuximab and the **ERGs** model estimates an overall survival gain of 4.5 months for encorafenib plus cetuximab. The ERG states that both the company and ERG base case estimates of overall survival demonstrate a difference of an average of at least 3 months additional overall survival for encorafenib plus cetuximab compared with FOLFIRI. However, it notes that it identified the risk of bias to be high or unclear for many aspects of the trial, therefore the magnitude of improvement is uncertain.
Why this issue is important	It is important to establish whether the end of life criteria is met for encorafenib plus cetuximab as it may impact the committee's decision making in terms of the cost-effectiveness estimates.
Technical team preliminary judgement and rationale	The results of the BEACON CRC trial suggest that encorafenib plus cetuximab increases survival by at least 3 months compared with the comparator arm of the trial. Both the company's and the ERG's models estimate a survival gain of over 3 months, however the results are uncertain.

4. Issues for information

Tables 10 to 12 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 10: ERG preferred assumptions and impact on the cost-effectiveness estimate, based on list price

Note: there are confidential commercial arrangements in place for encorafenib, cetuximab and trifluridine-tipiracil, analyses including the arrangements are confidential. The results presented in the table below are based on list price, estimates that include the commercial arrangements would be lower than those reported in the table.

Alteration	ERG rationale	Magnitude of change from company base case
Company base case	**–**	**£109,000***
1. ERG preferred approach to modelling overall survival: Kaplan-Meier data from BEACON CRC up to 2.8 months then extrapolation using an exponential curve	None of the parametric models offered an appropriate fit to the data, so a piecewise approach was used. Curve choice based on AIC BIC and clinical expert opinion. See issue 5.	
2. Applies the Kaplan-Meier curves from BEACON CRC trial for progression free survival	None of the parametric models offered an appropriate fit to the data, therefore Kaplan-Meier data were used. See issue 6.	
3. Applies the BEACON CRC trial FOLFIRI + cetuximab quality of life values for FOLFIRI	The trial data showed differences in health related quality of life values between the	

Alteration	ERG rationale	Magnitude of change from company base case
	treatments in the comparator arm of the BEACON CRC trial. See issue 7.	
4. Applies the BEACON CRC trial median relative dose intensities	The relative dose intensities in the BEACON CRC trial are skewed so the ERG applies the median values, the mean would underestimate cetuximab use. See issue 8.	
5. Assumes an initial loading dose for cetuximab, with the subsequent maintenance dose being on day 8, and thereafter fortnightly	Clinical expert opinion is split on the relevant dosing schedule for cetuximab in the first month. The ERG applies assumptions that include the loading dose plus 75% of the ongoing monthly cost. See issue 8.	
6. Revises the FOLFIRI grade 3+ adverse event costs to be based upon BEACON CRC, with an estimated [redacted] average cost per patient while also correcting the cell referencing error in the model implementation, the joint effect being to increase the FOLFIRI grade 3+ adverse event cost within the model	It is more consistent to apply the BEACON CRC FOLFIRI + cetuximab mean grade 3+ adverse events costs. The company base case estimate is £910.	
7. Revises PFS monthly resource use to have no additional administration costs, one outpatient consultation and for FOLFIRI two district nurse visits	Clinical expert opinion suggests monthly outpatient visits during progression free survival and that peripherally inserted central catheter resource use in the company submission seems high.	

Alteration	ERG rationale	Magnitude of change from company base case
8. Makes some minor corrections to the direct drug costs.	Given the cycle length the ERG thinks that the most appropriate method is to base direct drug costs on the proportion eligible for treatment at the start of the cycle and use a half cycle correction for benefits and QALYs.	
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate	–	
* The company's base case is based on list price, estimates that include the commercial arrangements would be lower than reported here.		

Table 11: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Limited data on BRAF mutation	There is limited data on the population with BRAF V600E mutation positive colorectal cancer. This poses several issues in modelling the cost-effectiveness of encorafenib plus cetuximab, including difficulty in validating any of the survival modelling results using natural history data.	It is not possible to externally validate the results of the economic modelling.
No evidence directly comparing encorafenib with relevant comparators	Cetuximab is included in all trial arms of the BEACON CRC trial. Cetuximab is not recommended in the UK for treating metastatic colorectal cancer beyond first line. Therefore, there is no evidence directly comparing encorafenib plus cetuximab with the comparators in the scope, FOLFIRI, irinotecan or trifluridine-tipiracil.	The relative effectiveness results are highly uncertain and the source of effectiveness data has a big impact on the ICER. Results of the cost-effectiveness analyses for encorafenib plus cetuximab compared with current practice are therefore highly uncertain.

Table 12: Other issues for information

Issue	Comments
Initiating cetuximab: dosing schedule	The summary of product characteristics for cetuximab specifies an initial dose of 400 mg/m^2 body surface area, followed by subsequent doses of 250 mg/m^2. However, the cancer drugs fund guidance from NHS England recommends a maintenance dosing schedule of 500 mg/m^2 every 2 weeks. Clinical experts in their statement to NICE suggest that in clinical practice the dosing schedule of 500 mg/m^2 given every 2 weeks is used. Further, during the COVID-19 pandemic the pragmatic decision was made to endorse this dosing regimen. This is in line with NICE guideline 161 COVID-19 rapid guideline: delivery of systemic anticancer treatments, which recommends decreasing the frequency of immunotherapy regimens where possible. TA439 cetuximab and panitumumab for previously untreated metastatic colorectal cancer considered these 2 dosing regimens for cetuximab and that the 500 mg/m^2 dose is not within the marketing authorisation for cetuximab. The company for this appraisal presented a randomised phase II trial (CECOG/CORE2) that showed that the effectiveness of cetuximab given every 2 weeks or weekly may be the same as 250 mg/m^2 once weekly. The committee concluded that it would take into account the lower costs of administration in clinical practice.
Innovation	According to the company, encorafenib is a first-in-class oral, chemotherapy-free therapy for people with BRAF V600E mutant metastatic colorectal cancer. The company states that it will provide a 'step change' in treatment of BRAF-mutant colorectal cancer.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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Technical engagement response form

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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 questions below. You do not have to answer every question. 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 summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5:00pm, 13 July 2020**

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 technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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.
- 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 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information 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	**Andrew Poll**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Pierre Fabre**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NA**

Questions for engagement

Issue 1: Treatment pathway	
Where would encorafenib plus cetuximab likely be used in NHS clinical practice? Is 2nd line the only relevant position for the committee to consider in their decision making?	**1.1. Response** The marketing authorisation for encorafenib with cetuximab is for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E-mutation, who have received prior systemic therapy. The marketing authorisation for encorafenib is supported by evidence from the Phase 3 study BEACON, in which adult patients with metastatic colorectal cancer harbouring a BRAF V600E-mutation were enrolled, whose disease had progressed following 1 or 2 prior regimens; around two-thirds of patients had received 1 prior regimen. Sub-group analysis showed there to be no variation in effect (Overall survival) by number of prior regimens. Overall, the licence and evidence base support the potential for encorafenib with cetuximab to be used at 2nd-line or 3rd-line. With regard to trifluridine-tipiracil the clinical experts consulted by NICE (Technical engagement papers page 459; page 477) highlight that this treatment would be used following exposure to other chemotherapy options, either at 2nd-line if all chemotherapy options are given in one regimen (as FOLFOXIRI) or at 3rd-line if given sequentially (e.g. FOLFOX 1st-line and FOLFIRI at 2nd-line). It is anticipated that if encorafenib with cetuximab were found not to be cost-effective as a 2nd-line regimen versus FOLFIRI, then by elimination the relevant comparator would be trifluridine-tipiracil in limited use as a 2nd line regimen or at 3rd-line.
Is single agent irinotecan an established 2nd line treatment for people with BRAF V600E mutation-positive metastatic colorectal cancer?	**1.2. Response** As highlighted in the company submission (Technical engagement papers page 11), the company maintains that single-agent irinotecan is not a relevant comparator after first-line treatment; patient-level data collected within the Systemic Anti-Cancer Therapy (SACT) dataset showed that single-agent irinotecan accounted for only 1.8% of therapies used at 2nd-line by patients. The clinical experts consulted by NICE (Technical engagement papers page 458; page 477) appear to support this view, highlighting that the use of single-agent irinotecan has largely been replaced by FOLFIRI.

Is best supportive care a relevant comparator for people with previously treated BRAF V600E mutation-positive metastatic colorectal cancer?	**1.3. Response** As highlighted in the company submission (Technical engagement papers, page 11), Pierre Fabre maintains that best supportive care is not a relevant comparator for encorafenib with cetuximab at 2nd- or 3rd-line. Best supportive care refers to supportive care to manage the symptoms and complications of the condition, when patients have exhausted all active treatment options (due to failure, lack of tolerability or contraindicated). The anticipated use of encorafenib with cetuximab would be earlier in the treatment pathway, where active treatments are still available (i.e. FOLFIRI or trifluridine-tipiracil). The clinical experts consulted by NICE (Technical engagement papers page 458; page 477) appear to support this view.
Where in the treatment pathway is trifluridine-tipiracil used? Is trifluridine-tipiracil a relevant comparator for encorafenib plus cetuximab?	**1.4 Response** See ***1.1 Response***.

Issue 2: Relevant comparators	
Does having a larger proportion of refractory patients in the RECOURSE trial have an impact on survival outcomes when compared to the BEACON CRC trial?	**2.1 Response** In the absence of any BRAF-mutant data for trifluridine-tipiracil, Pierre Fabre were limited to using the RECOURSE study as a proxy for the efficacy of trifluridine-tipiracil in a naïve comparison. This trial enrolled patients with metastatic colorectal cancer with mixed genetic characteristics (RAS wild-type and RAS mutant; BRAF status not specified) and a range of prior regimens from 2 to more than 4. Although this highlights a certain heterogeneity with the BEACON study in which patients had 1 or 2 prior regimens, the ERG's assertion that the much higher number of previous treatments in the RECOURSE trial likely biases substantially in favour of encorafenib dual therapy appears unlikely with further interrogation of the data. Subgroup data from the RECOURSE trial shows that trifluridine-tipiracil is progressively more effective with later lines of therapy when expressed relative to placebo; following 2 prior regimens (where the encorafenib regimen could be used), trifluridine-tipiracil appears similar to best supportive care (placebo arm) with a hazard ratio for overall survival with trifluridine-tipiracil vs placebo being 1.05 (95% confidence interval: 0.68, 1.63). In contrast, the hazard ratio was 0.74 (95% confidence interval: 0.51, 1.08) after 3 prior regimens and 0.59 (95% confidence interval: 0.47, 0.73) after 4+ prior regimens (*Mayer 2015*). By contrast the effectiveness of encorafenib with cetuximab is consistent regardless of line of therapy (1 or 2 prior regimens) (Company submission appendix D page 115). **'academic/commercial in confidence information removed'** (compared with 7.1 and 5.3 months, respectively for the overall trial population) **'academic/commercial in confidence information removed'** (Figure 1). Figure 1: **'academic/commercial in confidence information removed'** This data supports conclusions from a post-hoc analysis of RECOURSE published in 2019 which revealed that trifluridine-tipiracil performed better in the presence of markers for good prognosis such as low tumour burden, indolent disease, and absence of liver metastases, and the presence of these good prognostic characteristics may explain the better efficacy observed in later lines of therapy (*Tabernero 2019*). In contrast the presence of BRAF V600E mutation has been identified as one of the worse prognostic factors in patients with metastatic colorectal cancer (*Caputo 2019*), and the presence of this mutation was not measured in the RECOURSE, although based on the epidemiology of RAS and BRAF, it is likely that only 5% of patients harboured a BRAF mutation (Company submission, Technical engagement papers, page 69).

	Considering these points it is highly unlikely that the use of the RECOURSE study biases in favour of encorafenib dual therapy; on the contrary the evidence described above is suggestive of a poorer response of trifluridine-tipiracil when used following 2 prior regimens in a population consisting solely of BRAF-mutations. ***Revised economic analyses versus trifluridine-tipiracil*** A new economic analysis scenario using data from BEACON and RECOURSE for patients with 2 prior regimens is presented in ***11.2 Response***. References *Mayer 2015:* Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-19 *Tabernero 2019:* Tabernero J, Sobrero A, Borg C, et al. Exploratory analysis of the effect of FTD/TPI in patients treated in RECOURSE by prognostic factors. Journal of Clinical Oncology. 2019;37(no. 4_suppl):677. *Caputo 2019:* Caputo F, Santini C, Bardasi C, et al. BRAF-Mutated Colorectal Cancer: Clinical and Molecular Insights. Int J Mol Sci. 2019 Oct 28;20(21).
Are outcomes of patients who have previously received EGFR inhibitors expected to differ from patients who are EGFR naïve? Does this differ by place in the treatment pathway?	**2.2 Response** We are not aware of evidence available to directly demonstrate if outcomes of patients who have previously received epidermal growth factor receptor inhibitors would be expected to differ from patients who are epidermal growth factor receptor inhibitor naïve, or if this may differ by line of therapy.
Are the RECOURSE data used in the economic modelling robust and appropriate for decision making?	**2.3 Response** In considering how to compare encorafenib with cetuximab and trifluridine-tipiracil for our company submission there were three stepwise considerations, and we would reiterate these here alongside additional evidence: 1. Is there any evidence for trifluridine-tipiracil in BRAF-mutant metastatic colorectal cancer? 2. Is there any appropriate evidence for trifluridine-tipiracil in a broader population of patients with metastatic colorectal cancer?

	3. Is this evidence directly comparable or does it need to be adjusted in the knowledge that BRAF-mutations confers a much poorer prognosis on patients versus those without these mutations? In answer to question 1, and as highlighted in the company submission (Company submission, Technical engagement papers, page 68), a systematic review of the literature did not identify any evidence for trifluridine-tipiracil specifically in a population of patients with BRAF V600E-mutant metastatic colorectal cancer, and as such an indirect treatment comparison was not possible. This might have been anticipated given the relative rarity of the BRAF-V600E mutation in metastatic colorectal cancer and the absence of any Phase 3 trials providing evidence for effective treatment regimens for this hard-to-treat population. In answer to question 2, we broadened the inclusion criteria to consider trials in populations for whom BRAF mutation status had not been determined and presented survival curves that could be directly implemented in the economic model (Company submission, Technical engagement papers, page 68). Of three trials identified, two were solely in Asian populations, while the RECOURSE trial was conducted globally and comprised the largest patient population (N=800). As a result, and in the absence of BRAF-mutant specific evidence, the RECOURSE study was selected as the most appropriate to act as a proxy for trifluridine-tipiracil efficacy in a BRAF-mutant population. This decision was made while recognising the limitations of conducting a naïve comparison using two studies of heterogeneous populations (BEACON and RECOURSE) and is an obvious concern for the ERG. However, the concern of the ERG that the more refractory nature of the population enrolled in the RECOURSE trial (2, 3 or 4+ prior regimens) would likely bias in favour of encorafenib with cetuximab when both treatments are used following 2 prior regimens, we believe, is countered by our response above (***2.1. Response***). On the contrary, the evidence from RECOURSE suggests that a poorer response is expected with trifluridine-tipiracil when used earlier in the treatment pathway following 2 prior regimens, compared with 3 or 4+ prior regimens, and that poorer response is driven by the presence of poor prognostic factors, as highlighted by *Tabernero 2019*. In answer to question 3, we hypothesised that the efficacy of trifluridine-tipiracil would be worse in a BRAF-mutant population versus one of BRAF wild-type, given that BRAF mutations have been identified as one of the key drivers of poor prognosis in patients with metastatic colorectal cancer (*Caputo 2019*), and several studies have investigated the detrimental impact of BRAF mutation on outcomes. In our submission we concluded that the survival curves from RECOURSE wouldn't accurately reflect the efficacy of trifluridine-tipiracil in a BRAF-mutant population (Company submission, Technical engagement papers, page 69). We therefore applied hazard ratios for the relative impact of BRAF mutation versus BRAF wild-type to the survival curves from RECOURSE to adjust for this poorer prognosis. Using studies identified in our systematic literature review we selected a study by Peeters et al (*Peeters 2015*) for our base-case, as it was the only one that provided hazard ratios for both overall survival and progression-free survival; this study estimated that the hazard ratio for BRAF-mutant versus BRAF wild-

type for overall survival and progression-free survival were 4.00 and 3.56, respectively, demonstrating the substantially poorer prognosis in a BRAF-mutant population.

We recognise that this is a single study comparing two regimens, (FOLFIRI versus FOLFIRI with panitumumab) and that there may be potential for differences in the relative sensitivity of different treatments to the presence of BRAF mutations. In our submission (Company submission, Technical engagement papers, page 168) we also provided an economic scenario analysis in which data was taken from a systematic literature review and meta-analysis of 26 cohort and RCT studies (*Safaee Ardekani 2012*). Although the absolute impact on overall survival was less substantial, given the broad sample set this is not surprising; however the hazard ratio still indicates a substantial detrimental impact of BRAF-mutation (2.24 for BRAF mutant versus BRAF wild-type) and was statistically significant ($p<0.0001$).

This data should provide reassurance that:
1. BRAF mutation clearly confers a substantially poorer prognosis.

2. Poorer prognosis is observed for a range of different chemotherapy treatments, including combination treatments (e.g. FOLFIRI), and given that trifluridine-tipiracil is a single-agent chemotherapy drug it would seem reasonable to assume at least similar magnitude of reduction in efficacy for trifluridine-tipiracil in BRAF-mutant disease.

3. In the absence of other data, it would be appropriate for decision making purposes to expect that the efficacy of trifluridine-tipiracil would likely be substantially reduced.

Revised economic analyses versus trifluridine-tipiracil

A set of revised economic analyses for encorafenib with cetuximab versus trifluridine-tipiracil are provided in ***11.2 Response***.

References

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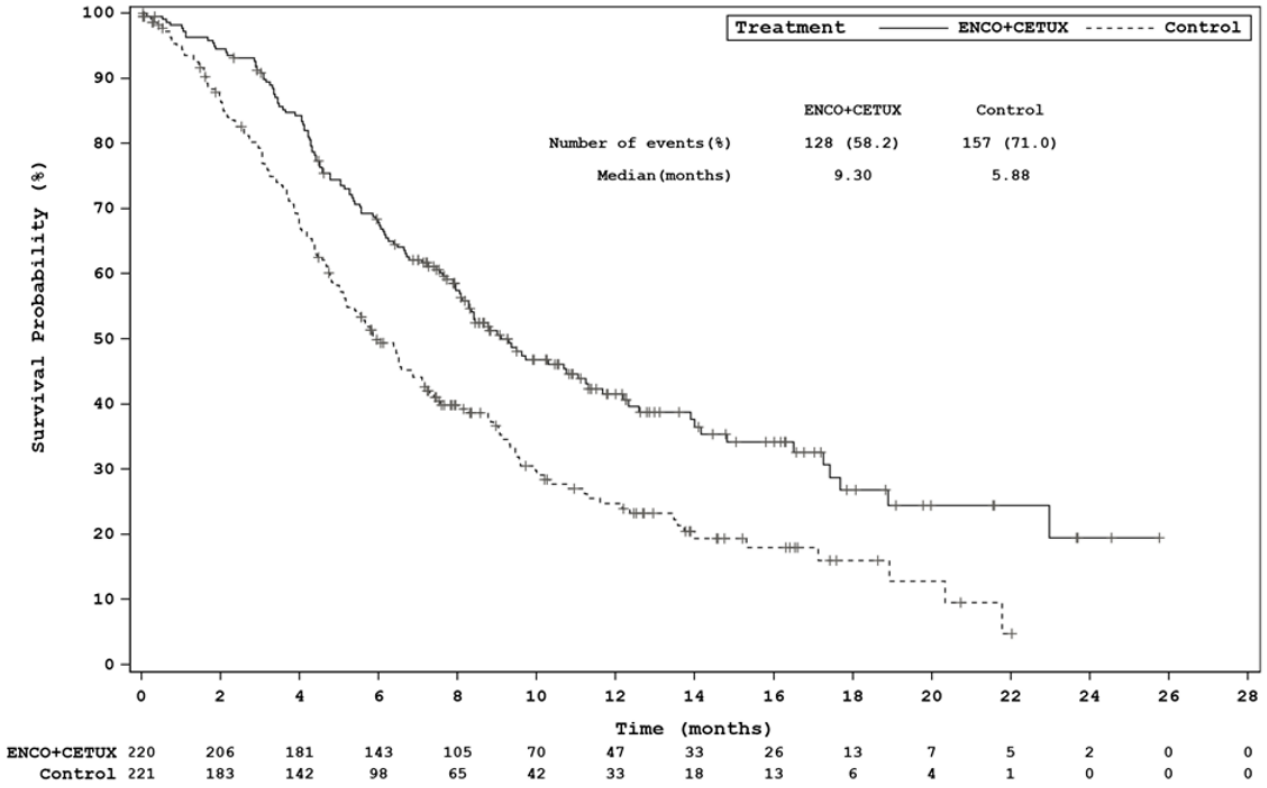
Issue 3: Indirect treatment comparison	
Is FOLFIRI equivalent to irinotecan in terms of clinical effectiveness? Would efficacy of either treatment be different in the BRAF-mutant population compared to wildtype?	**3.1 Response** As highlighted in the company submission (Company submission, Technical engagement papers, page 65), equivalence was assumed between FOLFIRI and irinotecan, based on evidence from two clinical trials (not BRAF-mutant). Although we are not aware of any evidence specifically in a BRAF-mutant population, equivalence was supported by expert clinical opinion elicited by Pierre Fabre during the submission process. The clinical experts consulted by NICE (Technical engagement papers, page 457; page 476) also appear to support this view of equivalence. During the clarification stage, we provided Kaplan-Meier survival curves (overall survival and progression-free survival) for the BEACON control arm split out by the chemotherapy regimens used, namely FOLFIRI with cetuximab and irinotecan with cetuximab. The BEACON trial was set up on the basis of equivalence between the two chemotherapy regimens, and whilst the trial was not powered to detect differences between the two components of the control arm, as would have been anticipated, these curves were broadly aligned.
Is cetuximab equivalent to panitumumab in terms of clinical effectiveness?	**3.2 Response** As highlighted in the company submission (Company submission, Technical engagement papers, page 65), equivalence was assumed based on a class effect (both are epidermal growth factor receptor inhibitors) and expert clinical opinion elicited by Pierre Fabre during the submission process. Furthermore, NICE concluded that these treatments were likely to have similar effectiveness in treating RAS wild-type mCRC during TA439 and the clinical experts consulted during that appraisal considered the two therapies to be equally effective. The clinical experts consulted by NICE for this current appraisal (Technical engagement papers, page 457; page 476) also appear to support this view of equivalence.

Issue 4: BEACON CRC trial as a proxy for estimating relative effectiveness	
Is cetuximab clinically effective for people with previously treated BRAF V600E mutation-positive metastatic colorectal cancer?	**4.1 Response** As with other therapies currently used to treat patients with BRAF-mutant metastatic colorectal cancer, the evidence for cetuximab is limited. Two published meta-analyses cited by the ERG (Technical engagement papers, page 533) highlight the lack of data (*Pietrantonio 2015; Rowland 2015*). Neither showed statistically significant benefit, although analyses were under-powered, with small sample sizes generating estimates with wide confidence intervals. However, the numerical benefit was always in favour of epidermal growth factor receptor inhibitors for progression-free survival and overall survival versus chemotherapy or best supportive care alone (*Pietrantonio 2015:* overall survival hazard ratio 0.91, 95% CI 0.62, 1.34, p=0.63; progression-free survival hazard ratio 0.88, 95% CI 0.67, 1.14, p=0.33; *Rowland 2015:* overall survival hazard ratio 0.97, 95% CI 0.67, 1.41, p=0.88; progression-free survival hazard ratio 0.86, 95% CI 0.61, 1.21, p=0.38). Analyses in a subset of patients with previously treated BRAF mutant disease similarly generated results that were not statistically significant (overall survival hazard ratio 1.06, 95% CI 0.48, 2.36, p=0.88; progression-free survival hazard ratio 0.84, 95% CI 0.46, 1.51, p=0.55) and suffered even more so through being under powered. The uncertainty generated by small sample sizes limits the interpretation of the analyses but an additive, albeit minimal benefit may be anticipated, based on feedback from the clinical experts engaged by NICE. The clinical expert representing the professional organisation submission (Technical engagement papers, page 442) stated that “we do know from studies such as CRYSTAL that these patients do benefit from cetuximab but it’s just they benefit less than the wild type population.” In addition, another clinical expert highlighted (Technical engagement papers, page 477), based on pre-clinical models, that the beneficial effect of encorafenib relies on the presence of cetuximab to dampen the feedback loop that BRAF inhibition alone would otherwise activate. References *Pietrantonio 2015:* Pietrantonio F, Morano F, Corallo S, Miceli R, Lonardi S, Raimondi A, et al. Maintenance Therapy With Panitumumab Alone vs Panitumumab Plus Fluorouracil-Leucovorin in Patients With RAS Wild-Type Metastatic Colorectal Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncology. 2019;03:03. *Rowland 2015:* Rowland A, Dias MM, Wiese MD, Kichenadasse G, McKinnon RA, Karapetis CS, et al. Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. Br J Cancer. 2015;112(12):1888-94.

Issue 5a: Modelling overall survival for BEACON CRC encorafenib plus cetuximab data	
For people who have had previous treatment for metastatic BRAF-V600E mutation positive colorectal cancer, and received encorafenib plus cetuximab what proportion would you expect to survive to 3 and 5 years?	**5.a.1 Response** The August 2019 data cut from BEACON was the final and most mature *formal* analysis available. This data cut was presented as the key clinical evidence in the company submission and was used in company base-case economic analyses. This dataset generated an overall survival Kaplan-Meier for encorafenib/cetuximab with a maximum follow-up of 26 months, as shown in Figure 2. **Figure 2: BEACON study overall survival for encorafenib with cetuximab versus control – Kaplan-Meier, data cut-off August 2019** 

Among the parametric models fitted to the overall survival curve, log-logistic and Weibull parametric models were validated visually by oncology experts as providing clinically plausible estimates of long-term survival. The Weibull model was seen as overly pessimistic by some experts (12.7% alive at 2 years; 3.1% alive at 3 years; <1% alive at 5 years) and given that the log-logistic had the best statistical fit this was used as company base case (Estimated 17.7% alive at 2 years; 9.8% alive at 3 years; 4.4% alive at 5 years). Conversely in the ERG report which used alternate methods to fit the curves from 2.8 months onwards, the ERG argued that the log-logistic was probably too optimistic and opted for the most pessimistic outcome (Exponential: 14.7% alive at 2 years, 5.2% alive at 3 years, 0.7% alive at 5 years) (Technical engagement papers, page 563).

Following the ERG report, Pierre Fabre conducted a further exploratory analysis, utilising the latest available data up to May 2020, with a maximum follow up for overall survival of around **'academic/commercial in confidence information removed'** months. Although this analysis was not planned and is subject to further data cleaning, this now represents the most mature dataset available, and provides further certainty as to the longer-term outcomes for patients treated with encorafenib/cetuximab. As shown in Figure 3, the new data cut provides additional certainty to the overall survival curve between 12 and 24 months with many more patients at risk (e.g. at month 18, **'academic/commercial in confidence information removed'** versus 13 for encorafenib with cetuximab) and many more events occurring in that period (each denoted by a step in the Kaplan-Meier curve). This new dataset provides estimated 2-year survival of **'academic/commercial in confidence information removed'**% in the encorafenib/cetuximab group.

This more mature dataset provides further validation for the log-logistic curve fitted to the original August 2019 dataset, for which 2-year survival of 17.7% was predicted (See Figure 4) and shows this was accurate in predicting subsequent events. It also supports the view that the ERG's preferred piecewise/exponential curve was unnecessarily pessimistic and potentially now lacks face validity since it estimated only around 14.7% survival at 2 years and 5.2% at 3 years.

When fitting parametric curves to the updated May 2020 dataset, log-logistic again is the best fit statistically, and provides 2-, 3- and 5-year estimates of survival of **'academic/commercial in confidence information removed'**, respectively in the encorafenib/cetuximab group (See Figure 5). Furthermore, the magnitude of the treatment effect on overall survival was also maintained between data cuts, as shown by the hazard ratio for encorafenib/cetuximab versus control (**'academic/commercial in confidence information removed'**). It therefore appears reasonable to assume that this treatment effect is maintained for the period beyond the observed data.

Figure 3: BEACON study overall survival for encorafenib with cetuximab versus control – Kaplan-Meier, data cut-off May 2020 'academic/commercial in confidence information removed'

Figure 4: Comparison of encorafenib with cetuximab overall survival curves – BEACON Kaplan-Meier data cut-off May 2020 vs company log-logistic on August 2019 data cut-off vs ERG piecewise exponential on August 2019 data cut-off
'academic/commercial in confidence information removed'
Abbreviations: E+C, encorafenib with cetuximab; ERG, evidence review group; KM, Kaplan-Meier.

Figure 5: Comparison of encorafenib with cetuximab overall survival curves – BEACON Kaplan-Meier data cut-off May 2020 vs company log-logistic on May 2020 data cut-off
'academic/commercial in confidence information removed'
Abbreviations: E+C, encorafenib with cetuximab; ERG, evidence review group; KM, Kaplan-Meier.

Further validation of the long-term estimates of survival provided by parametric extrapolation beyond the extent of the BEACON CRC trial are clearly challenging. As a new targeted therapy which acts via a different mechanism of action to other treatments used in this patient population, encorafenib with cetuximab clearly demonstrated statistically significant improvements in overall survival and progression-free survival outcomes compared with clinician's choice of chemotherapy (FOLFIRI or irinotecan with cetuximab) and is the first trial conducted in previously treated patients with BRAF-mutant metastatic colorectal cancer who receive a targeted therapy. As such, there is no prior like-for-like evidence to enable the external validation of these projections. For example, examining populations of patients with BRAF-mutant metastatic colorectal cancer who have been treated with 1 or 2 prior lines of standard chemotherapy would clearly underestimate the long-term survival of patients treated with encorafenib/cetuximab.

Nunes 2020 recently presented overall survival data from a large unselected cohort of patients with metastatic colorectal cancer (*Nunes 2020*), including 86 with BRAF V600E mutation. Patients were treated with standard chemotherapy, including irinotecan-, oxaliplatin- and fluorouracil-based regimens, across various line of therapy from 1st-through to 5th-line. The study reported survival data for a follow-up period of around 4.5 years after diagnosis for patients with BRAF mutations receiving treatment. Visual inspection of the overall survival curve for patients treated with 1st-line chemotherapy shows an overall survival estimate of around 20% at 2 years (Nunes 2020, Figure 2D), which is similar to that observed in BEACON with the May 2020 dataset. Longer-term estimates taken visually from the Nunes overall survival curve suggest 3-year and 4-year estimates of around 12% and 5%, respectively. Clearly these patients are not directly comparable to BEACON given the different lines of therapy that patients are receiving, however the trajectory of the Nunes curve from 2 years onwards provides some external validity to the trial-based outcomes observed in BEACON and long-term estimates generated by the log-logistic parametric curve fit we adopted.

	Revised economic analyses versus FOLFIRI A set of revised economic analyses for encorafenib with cetuximab versus FOLFIRI which utilise the May 2020 data cut-off are provided in ***11.1 Response***. Parametric curve fits on the encorafenib/cetuximab overall survival curve from May 2020 data cut are shown in Figure 6. Log-logistic is the best fit statistically, with AIC being >3 units better than other models. Log-logistic, along with the next best fits in terms of AIC (Lognormal and generalised gamma) provide similar trajectory and all represent consistent predictions of long-term outcomes. In line with the best fit statistics, log-logistic was selected for revised economic analyses on May 2020 data, as presented throughout ***11. Response***. **Figure 6: Comparison of parametric models fitted to encorafenib with cetuximab overall survival Kaplan-Meier curves (BEACON data cut-off May 2020)** **'academic/commercial in confidence information removed'** Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion. References *Safaee Ardekani 2012:* Safaee Ardekani G, Jafarnejad SM, Tan L, Saeedi A, Li G. The prognostic value of BRAF mutation in colorectal cancer and melanoma: a systematic review and meta-analysis. PLoS One. 2012;7(10):e47054. *Nunes 2020:* Nunes L, Aasebo K, Mathot L, Ljungstrom V, Edqvist PH, Sundstrom M, et al. Molecular characterization of a large unselected cohort of metastatic colorectal cancers in relation to primary tumor location, rare metastatic sites and prognosis. Acta Oncol. 2020;59(4):417-26.
How informative is the ERG's analysis regarding the extrapolation of overall survival?	**5.a.2 Response** As described in ***5.1.a Response***, the availability of the more mature BEACON dataset provides more certainty in the outcomes observed within trial between year 1 and year 2, and alongside the longer-term real-world evidence of Nunes 2020, further validates the choice of the log-logistic parametric model in estimating the long-term outcomes projections that may be anticipated in patients treated with encorafenib/cetuximab. In contrast, the ERG's projections appeared overly pessimistic and did not appear to take account of the substantial additional benefit of this new regimen above standard chemotherapy. In this respect the ERG's method appears to fail to recognise the importance of taking an approach to selecting a parametric function that predicts overall survival in the period beyond the observed data, according to *appropriate* external data/expert opinion.

	The ERG critique also suggests that the shape of the Kaplan-Meier curves for overall survival is such that fitting a single parametric function to each randomised arm of the BEACON trial is problematic. They justify this by saying that the curves initially diverge, then converge, before diverging again. In samples of this size it may be unlikely that the shape of the curves would be perfectly smooth, a point that is made in NICE Decision Support Unit Technical Support Document 14 (*NICE DSU TSD14*) which states on page 19: "If censoring is heavy and observed data points are clustered at certain points along the Kaplan Meier curve, it might be quite reasonable for a parametric model to follow the Kaplan Meier closely for one segment, but not at another – such an occurrence does not necessarily mean that the model is inappropriate." In conclusion, we feel that our use of the fully parametric approach is most appropriate particularly given the availability of the May 2020 dataset from BEACON, but also recognise that the ERG's approach of fitting a parametric curve from 2.8 months onwards provides an alternate method. As such, in ***11 Response*** we present economic scenarios in which we examine the impact of fitting parametric models to the new May 2020 BEACON overall survival dataset from 2.8 months, but retain our base case using fully parametric curve fits. <u>References</u> *NICE DSU TSD14:* Latimer N. NICE Decision Support Unit Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

Issue 5b: Modelling overall survival for the comparator arm	
For people who have had previous treatment for metastatic BRAF-V600E mutation positive colorectal cancer, and receive current standard of care as 2nd line what proportion would you expect to survive to 3 and 5 years respectively?	**5.b.1 Response** There is a clear paucity of evidence for the effectiveness of cancer treatments for patients with BRAF-mutant metastatic colorectal cancer, in particular in those who have received prior treatment. Using the limited evidence available, we were able to conduct an ITC to generate our best estimate as the effectiveness of FOLFIRI, when taken alone. The ITC utilised a single study (*Peeters 2015*) which compared FOLFIRI versus FOLFIRI with panitumumab to generate a hazard ratio for the relative effect of encorafenib /cetuximab versus FOLFIRI. The hazard ratio was then applied to the parametric curve for encorafenib/cetuximab to generate an estimated survival curve for FOLFIRI. We recognise there is uncertainty in the estimates of FOLFIRI effectiveness generated in using the ITC, but we also maintain that using the control arm from BEACON would likely overestimate the survival estimates for FOLFIRI alone, given that the control arm included cetuximab. The uncertainty around the magnitude of effect observed when cetuximab is used in combination with other drugs has been covered in ***4.1 Response***.
Based on data presented is the company's approach to modelling overall survival appropriate?	In our analyses, using the more mature May 2020 BEACON dataset, to which the ITC hazard ratio is applied, generates estimates of survival for FOLFIRI of **'academic/commercial in confidence information removed'**% at year 1, **'academic/commercial in confidence information removed'**% at year 2, **'academic/commercial in confidence information removed'**% at year 3, with a median survival of **'academic/commercial in confidence information removed'** months. As highlighted in our company submission (Technical engagement papers, page 78) and replicated here in Table 1, median overall survival estimates for FOLFIRI identified in our company submission systematic literature review in BRAF-mutant metastatic colorectal cancer, range between 4.2 and 5.7 months. These are below that of the control arm from BEACON for which cetuximab was used in combination with the investigator's choice of chemotherapy (5.88 months August 2019 data cut; **'academic/commercial in confidence information removed'** months May 2020 data cut). Further examination of FOLFIRI studies which reported Kaplan-Meier survival curves (*Yoshino 2019; Wirapati 2017*) in BRAF-mutant populations provide limited additional information due to the small sample sizes enrolled. 1-year survival estimates by visual inspection of the curves are 18% and 15%, from Yoshino 2019 and Wirapati 2017, respectively, although numbers at risk at this time point are limited in both studies (n≤6). These 1-year estimates of survival are above those generated by our ITC but substantially below those observed for the BEACON control arm (May 2020: **'academic/commercial in confidence information removed'**%).

Table 1: Comparison of outcomes in selected studies reporting BRAF-mutant mCRC populations

Study/ reference	Line of therapy	Intervention	N	Median OS (months)
BEACON CRC	≥2	FOLFIRI with cetuximab or irinotecan with cetuximab	221	**'academic/commercial in confidence information removed'†**
20050181 (*Peeters 2015*)	2	FOLFIRI	45‡	5.7
RAISE (*Yoshino 2019*)	2	FOLFIRI + placebo	21	4.2
VELOUR (*Wirapati 2017*)	2	FOLFIRI + placebo	36‡	5.5

Abbreviations: NR, not reported; OS, overall survival.
† August 2019 data cut, with May 2020 data cut in parentheses; ‡ N is for overall BRAF-mutant subgroup treated across two treatment arms.

Revised economic analyses versus FOLFIRI

Recognising the uncertainty in estimating the effectiveness of FOLFIRI, we have provided revised economic analyses in ***11.1 Response*** for encorafenib with cetuximab versus FOLFIRI. For base-case, we continue to use the ITC, and provide a scenario which uses the BEACON control arm as a proxy for FOLFIRI. All analyses utilise the new May 2020 dataset from BEACON.

References

Peeters 2015: Peeters M, Oliner KS, Price TJ, Cervantes A, Sobrero AF, Ducreux M, et al. Analysis of KRAS/NRAS Mutations in a Phase III Study of Panitumumab with FOLFIRI Compared with FOLFIRI Alone as Second-line Treatment for Metastatic Colorectal Cancer. Clin Cancer Res. 2015;21(24):5469-79.

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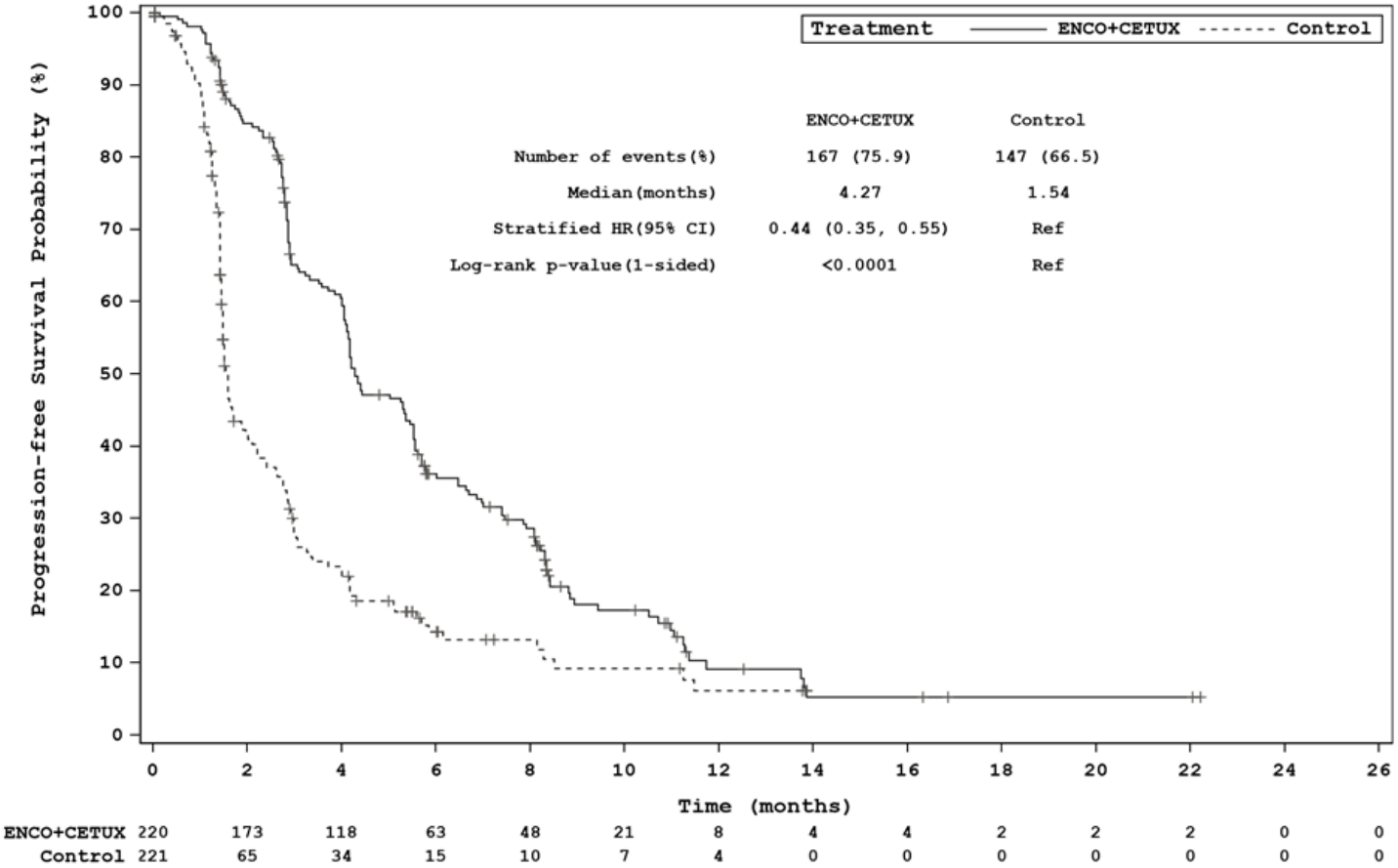
Issue 6: Modelling progression free survival	
What proportion of patients would be expected to remain progression free at 3 years after having had encorafenib plus cetuximab?	**6.1 Response** As acknowledged in ***5.a.1 Response***, estimating long-term progression-free survival using the published literature for existing treatments would likely underestimate the outcomes that could be achieved with encorafenib/cetuximab, because the BEACON study has demonstrated that the encorafenib regimen leads to statistically significant improvements versus standard chemotherapy regimens. As such, the most robust evidence available would most likely come from BEACON and extrapolation of this dataset beyond the trial period. The ERG notes in their report (Technical engagement papers, page 564) that our approach to modelling progression free survival results in at least 1% of patients on encorafenib plus cetuximab remaining in the progression free health state for up to 3.4 years, considerably longer than the current follow-up of the BEACON trial. The maximum observed follow-up time in the August 2019 data cut from BEACON was around 22 months, at which point the Kaplan-Meier plot from the trial BEACON estimates 5.3% of patients remain progression-free (Figure 7). As described in ***5.a.1 Response***, a more mature dataset is now available from BEACON. For progression-free survival, maximum follow-up has extended out to just over 30 months (Figure 8) in the encorafenib/cetuximab arm, at which point **'academic/commercial in confidence information removed'**% of patients remain progression-free. Parametric curve-fits to this updated dataset generate an estimate of progression-free survival at 3 years of **'academic/commercial in confidence information removed'**%, based on a log-logistic model.

Figure 7: BEACON study progression-free survival for encorafenib with cetuximab versus control – Kaplan-Meier, data cut-off August 2019



Abbreviations: CI, confidence interval; HR, hazard ratio.

	Figure 8: BEACON study progression-free survival for encorafenib with cetuximab versus control – Kaplan-Meier, data cut-off May 2020 **'academic/commercial in confidence information removed'**
Is the ERG's approach to modelling progression free survival appropriate?	**6.2 Response** We recognise the alternate approach taken by the ERG to model progression-free survival by using the Kaplan-Meier from BEACON rather than applying parametric models. As shown in the ERG report (Technical engagement papers page 593) the ERG approach appears to generate ICERs that are more favourable for the encorafenib regimen than the company approach. The maturity of the May 2020 dataset should add more certainty to the progression-free survival data used to inform the economic model. Nevertheless, our original approach, we believe, is in line with NICE Decision Support Unit Technical Support Document 14 (*NICE DSU TSD14*) which would be to choose a parametric survival function that gives the most plausible predictions, and not to rely entirely on the trial data. To remain consistent with our original approach and allow extrapolation beyond the follow-up of the trial our revised economic analyses are based on a fully parametric approach. References *NICE DSU TSD14:* Latimer N. NICE Decision Support Unit Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011.

Issue 7: Modelling time to treatment discontinuation	
Is it appropriate to assume that time to treatment discontinuation is the same as progression free survival for encorafenib plus cetuximab and the relevant comparators?	**7.1 Response** We maintain that our decision to model progression-free survival as a proxy for time on treatment was a valid, evidence-based approach, which was driven by data from BEACON (Company submission, Technical engagement papers, page 122) showing that time to discontinuation and progression-free survival curves are not statistically different (p=0.46 encorafenib plus cetuximab and p=0.19 control) and 95% confidence intervals overlap. The approach was corroborated by feedback from clinical experts who stated that the assumption that progression-free survival is equal to time on treatment is reflective of current clinical practice. In other words, patients would come off treatment once they had progressed. Furthermore, time to treatment discontinuation data were only available for the BEACON trial, and not from the indirect treatment comparison, which precluded their use in our company base-case (i.e. time to treatment discontinuation could only have been used for the encorafenib arm). ***Revised economic analyses*** The majority of our revised economic analyses (base-case and various scenarios) in this response retain progression-free survival as a proxy for time on treatment and these are provided in ***11.1 Response***. In addition, as requested within the technical report we provide a separate standalone scenario to show how the cost-effectiveness estimate compares when using time to treatment discontinuation versus progression-free survival to model time on treatment. The following assumptions apply for this scenario: • Since we use the indirect treatment comparison for our base-case for which we do not have time to treatment discontinuation data, this standalone scenario is conducted on outcomes data from both arms of the BEACON trial, such that encorafenib/cetuximab is compared with the control arm. • Outcomes data for overall survival, progression-free survival and time to treatment discontinuation are derived from the August 2019 BEACON dataset since time to treatment discontinuation data isn't available from the May 2020 dataset. • A Weibull model was the best statistical fit for time to treatment discontinuation data as an average across the two arms of BEACON (See Table 2). • List prices are used for all drug prices, to make comparisons with the ERG's analyses easier. • ICER 1 is generated using progression-free survival as the proxy for time on treatment for both model arms, whereas ICER 2 is generated using time to treatment discontinuation.

- The results show that when the control arm from BEACON is used to inform the outcomes for FOLFIRI, the ICER is reduced when using time to treatment discontinuation versus progression-free survival for time on treatment (Table 3). Note that, as described above, this is only applicable to the scenario in which the control arm is used as a proxy for FOLFIRI effectiveness and cannot be applied to the base-case analysis in which the indirect treatment comparison is used to inform the effectiveness of FOLFIRI.

Table 2: AICs for the parametric models fit to BEACON time to treatment discontinuation data; August 2019 data cut

Model	Encorafenib with cetuximab	Control	Mean
Generalised gamma	1100.746	728.555	914.651
Weibull	1098.759	726.999	912.879
Exponential	1109.872	727.280	918.576
Log-logistic	1113.360	743.756	928.558
Lognormal	1143.927	756.157	950.042
Gompertz	1103.640	726.240	914.940

Abbreviations: AIC, Akaike information criterion.

Table 3: Economic scenario assessing impact of using progression-free survival or time to treatment discontinuation for time on treatment; BEACON August 2019 data cut

Analysis	E+C cost (£)	F cost (£)	E+C LYG	F LYG	E+C QALYs	F QALYs	Δ cost (£)	Δ LYG	Δ QALYs	ICER
ICER 1: Time on treatment = PFS	£68,809	£13,543	1.362	0.963	0.917	0.640	£55,266	0.399	0.277	£199,161
ICER 2: Time on treatment = Weibull curves fit to BEACON time to treatment discontinuation	£64,411	£13,202	1.362	0.963	0.917	0.640	£51,209	0.399	0.277	£184,538

Abbreviations: Δ, incremental; E+C, encorafenib with cetuximab; F, FOLFIRI; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PF, Pierre Fabre; PFS, progression-free survival; QALY, quality-adjusted life year.

Issue 8: Utility values	
Are the utility values included in the company model appropriate?	**8.1 Response** ***Revised economic analyses*** See ***11.1 Response***, highlighting the company's revised approach to deriving utility values for revised economic analyses. This revised approach is in line with the preferred approach of the NICE technical team and the ERG.

Issue 9: Cost uncertainties in the analysis	
What is the correct dosage of cetuximab in clinical practice?	**9.1 Response** As summarised in Table 12 (page 42) of the Technical report, the NHSE Cancer Drugs Fund guidance for the use of cetuximab for patients with metastatic colorectal cancer states that "Cetuximab will be given as a 2-weekly regimen at a dose of 500 mg/m^2", whereas the summary of product characteristics for cetuximab specifies an initial dose of 400 mg/m^2 body surface area, followed by subsequent weekly doses of 250 mg/m^2. The most recent NHSE Cancer Drugs Fund guidance, as at 3rd July 2020 remains consistent with this approach (*NHSE Cancer Drugs Fund 2020*), while NICE Guideline 161 "COVID-19 rapid guideline: delivery of systemic anticancer treatments", section 7.2 recommends decreasing the frequency of immunotherapy regimens where possible (*NICE guideline 161*). As highlighted in the company submission (Company submission, Technical engagement papers, page 14) and confirmed by both of NICE's clinical experts and one of the ERG's clinical experts (Technical engagement papers page 459, 478, 577), the NHSE guidance should reflect clinical practice in England, and in the view of Pierre Fabre is the most appropriate approach to take to costing cetuximab. The approach taken originally by Pierre Fabre included, in error, the 400 mg/m^2 initiation dose as well as the 500 mg/m^2 maintenance dose. Using the revised approach of a 2-weekly regimen of cetuximab 500 mg/m^2 results in a cetuximab cost which is greater than that used in the original company submission but lower than that utilised by the ERG, and is likely to be most reflective of clinical practice in England. ***Revised economic analyses*** All new analyses provided in this technical engagement response use this updated approach to cetuximab costing (See ***11 Response***). References *NHSE Cancer Drugs Fund 2020:* NHS England. National Cancer Drugs Fund List ver1.165 27-May-20. 2020. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-ver1.165.pdf. *NICE guideline 161:* NICE. NICE guideline 161. COVID-19 rapid guideline: delivery of systemic anticancer treatments. 2020. Available from: https://www.nice.org.uk/guidance/ng161.

Do the differences in the relative dose intensities of cetuximab impact on the robustness of the cost-effectiveness estimates?	**9.2 Response** ***Mean versus median relative dose intensity*** The ERG highlights that the relative dose intensity data from the BEACON CRC trial is quite skewed, with the median relative dose intensity being somewhat higher than the mean. The ERG speculates that this is likely a result of 'some patients faring poorly in the early period of the trial' noting that those who remain in the trial have a better relative dose intensity (Technical engagement papers, page 578). The ERG suggests that applying the mean relative dose intensity would underestimate cetuximab use and applies median relative dose intensities for cetuximab instead of the mean. In the absence of other evidence to the contrary, our assumption would be that the mean is a better reflection of clinical practice, i.e. if a few patients fare poorly in the trial then it may be reasonable to assume the same in clinical practice. Pierre Fabre would welcome input from clinical experts on this issue. ***Revised economic analyses*** To aid the Appraisal Committee we have provided an economic scenario in which median relative dose intensities are applied rather than the mean (See ***11.1 Response***). ***Notification of error in relative dose intensity calculation*** In addition, we have noted an error which requires correction in order that the economic evidence can be correctly interpreted. The company model assumed that for oral treatment (i.e. encorafenib) the relative dose intensity was applied to account for temporary dose interruptions etc, however part pills were then rounded up to the nearest whole pill meaning that all patients accrued the cost of the full dose. So, if patients are given encorafenib 300 mg/day, when applying a mean relative dose intensity of **'academic/commercial in confidence information removed'**%, they should receive an average of ~260 mg/day. However, because they are given 75 mg pills, the model then assumed 4 whole pills, thus 300 mg/day. In this way the temporary dose interruptions captured by applying the relative dose intensity and that may be seen in clinical practice, have not been accounted for and the cost of encorafenib is overestimated. We would propose that a more realistic scenario is to capture the cost associated with the mean relative dose intensity value, i.e. the cost of 260 mg/day. To reflect this in revised economic analyses, the relative dose intensity has been used as a weight for the number of tablets per administration, and any rounding of tablets to whole numbers has been removed.

	Revised economic analyses All new analyses provided in this technical engagement response use this updated approach to applying relative dose intensity for encorafenib (See ***11.1 Response)***.
Is the assumption of no drug wastage reasonable?	**9.3 Response** In our base-case we assumed that vial sharing would occur where possible (Form B page 129), as opposed to vial wastage where the remainder of an intravenous-administered drug would be discarded after use. This assumption was made following input from clinical experts, who stated that in clinical practice effort would be made to share vials between patients in order to minimise costs. ***Revised economic analyses*** To allow NICE to assess what the impact would be if vial sharing was not possible in all situations, we have provided a cost-effectiveness scenario for encorafenib/cetuximab versus FOLFIRI in which it is assumed that vial wastage occurs in 10% of patients (See ***11.1 Response***).

Issue 10: End of life criteria	
Does the evidence support that encorafenib plus cetuximab extends life by 3 months or more compared with current practice?	**10.1 Response** The technical team state that "The results of the BEACON CRC trial suggest that encorafenib plus cetuximab increases survival by at least 3 months compared with the comparator arm of the trial. Both the company's and the ERG's models estimate a survival gain of over 3 months, however the results are uncertain." (Technical Report, page 37). There are several points that should provide reassurance that encorafenib with cetuximab treatment would extend life expectancy by 3 months or more. Firstly, encorafenib with cetuximab was estimated to derive an improvement in median overall survival of 3.4 months over the investigators choice of control chemotherapy, within the setting of a large Phase 3, randomised regulatory trial designed specifically in the patient population of direct relevance to the proposed position of the encorafenib regimen in clinical practice. Secondly, the control arm included cetuximab which is anticipated to have an additional, if minimal benefit versus chemotherapy alone, such that versus FOLFIRI alone the additional life expectancy provided by the encorafenib regimen should be at least as big as that estimated by the BEACON trial. Thirdly, the level of optimism around the long-term outlook for patients with BRAF-mutant metastatic colorectal cancer varied substantially between our approach and that of the ERG and generated considerable uncertainty in the cost-effectiveness estimates generated for the encorafenib regimen. However, even when adopting the most pessimistic outlook of the ERG analyses still generated a mean survival benefit of 4.5 months. With the availability of the May 2020 data cut providing greater certainty to the overall survival estimates, the NICE Appraisal Committee should be more assured that life expectancy gains of at least 3 months are achievable with the encorafenib regimen.
Under standard care, is the life expectancy of adults with previously treated BRAF-V600E mutation positive metastatic colorectal cancer less than 24 months?	**10.2 Response** It is recognised that the prognosis for patients with metastatic colorectal cancer who harbour BRAF-mutations is extremely poor, and life expectancy is expected to be considerably shorter than 24 months; as per the company submission (Company submission, Technical engagement papers, page 91) the BEACON CRC study shows median overall survival with chemotherapy (FOLFIRI or irinotecan) in combination with cetuximab = 5.88 months. A number of other studies have demonstrated overall survival ranging between 4.2 and 5.7 months for FOLFIRI alone based on small sample BRAF-mutant subgroups examined in post first-line settings. Taken together these data support the limited life expectancy in patients with BRAF-mutant mCRC in a post 1st-line setting.

11 Response: Revised supporting economic analyses

We present a number of revised economic analyses versus FOLFIR and versus trifluridine-tipiracil that we hope will assist the Appraisal Committee in their decision making. All revised economic analyses take account of the points described below, reflecting new data from BEACON, specific preferences highlighted by the ERG or NICE technical team, and in one case a minor error from our original submission that requires correction.

- **Economic analyses versus FOLFIRI are provided in 11.1 Response:** Description of scenarios (Table 4), pairwise results (Table 6) and deterministic and probabilistic results for the revised base case in Figure 9, Figure 10 and Table 7.
- **Economic analyses versus trifluridine-tipiracil are described 11.2 Response:** Description of scenarios (Table 8), pairwise results (Table 9) and deterministic and probabilistic results for the revised base case in Figure 11, Figure 12 and Table 10.
- For ease of comparison, we also provide the ICER from our original company submission base-case, amended using drug list-prices (Table 6 and Table 9).

Revisions to all analyses

- **BEACON May 2020 data cut providing more mature outcomes data**
  - For the pivotal encorafenib Phase 3 trial, BEACON, the 15th August 2019 was the final and most mature *formal* analysis available and was presented as the key clinical evidence in the company submission and was used in company base-case economic analyses. Since submission, a further data cut as at May 2020 has become available. This was not planned and has not been formally tested statistically. However, this now represents the most mature dataset available and we now submit revised economic analyses using overall survival and progression-free survival data from this May 2020 data cut.
- **Utility values**
  - Revised approach:
    - ◊ FOLFIRI model arm: use utilities specific to FOLFIRI with cetuximab from BEACON control arm, rather than entire control arm.
    - ◊ Trifluridine-tipiracil model arm: use average of utilities for encorafenib with cetuximab arm from BEACON and FOLFIRI with cetuximab from control arm of BEACON.
  - Justification:
    - ◊ In the company submission for the FOLFIRI model arm we used utilities derived from the overall control arm of the BEACON study. In the Technical report (page 34), commenting on the encorafenib with cetuximab and FOLFIRI

economic analysis, the NICE technical team agrees with the ERG's approach of using utilities specific to FOLFIRI with cetuximab from the control arm of BEACON, rather than the overall control arm. Given the agreement between NICE and the ERG our revised economic analyses use the FOLFIRI/cetuximab specific utilities for the FOLFIRI model arm.

◊ In the absence of utility data specific to trifluridine-tipiracil, the company submission used the mean of the utilities for the encorafenib with cetuximab and control (FOLFIRI with cetuximab or irinotecan with cetuximab) arms from BEACON for trifluridine-tipiracil. To be consistent with our original approach, for trifluridine-tipiracil our revised economic analyses use the mean of utilities for encorafenib with cetuximab and FOLFIRI with cetuximab from BEACON.

- **Cetuximab cost in first treatment cycle**
  - Revised approach: maintenance dose of 500 mg/m^2 every 2 weeks (Day 1, Day 15), no initiation dose.
  - Justification: See ***9.1 Response***.
- **Relative dose intensity calculation error**
  - Revised approach & justification: Pierre Fabre noted an error in the relative dose intensity calculations used in our original submission/model which requires correction (described further in ***9.2 Response***).
- **Drug prices**
  - Revised approach & justification: to facilitate ease of comparison with ERG analyses all drug prices are presented as ***list prices***.

11.1 Response: Revised analyses versus FOLFIRI

Description of scenarios

Table 4: Key parameters for revised pairwise analyses versus FOLFIRI

Analysis	Key parameters/changes from company submission base case	Additional changes
Company submission base case	• Encorafenib with cetuximab: August 2019 overall survival & progression-free survival BEACON, fully parameterised log-logistic • FOLFIRI: ITC hazard ratio	• N/A
PF F1 Revised base-case	• Encorafenib with cetuximab: May 2020 overall survival & progression-free survival BEACON, fully parameterised log-logistic • FOLFIRI: ITC hazard ratio	• FOLFIRI utility values (FOLFIRI with cetuximab from BEACON control arm) • Cetuximab dosing (500 mg/m^2 every 2 weeks, no initiation dose)

Analysis	Key parameters/changes from company submission base case	Additional changes
		• Relative dose intensity correction • Drug list prices
PF F2 Scenario	• As PF F1 plus • FOLFIRI: BEACON control arm	• As PF F1
PF F3 Scenario	• As PF F1 plus • Encorafenib with cetuximab: May 2020 overall survival BEACON, use of KM curves to 2.8 months, followed by parameterised extrapolation (log-logistic) (progression-free survival remains as fully parametric as per base case)	• As PF F1
PF F4 Scenario	• As PF F1 plus • Encorafenib with cetuximab: May 2020 overall survival BEACON, use of KM curves to 2.8 months, followed by parameterised extrapolation (log-logistic) (progression-free survival remains as fully parametric as per base case) • FOLFIRI: BEACON control arm modelled as above for encorafenib/cetuximab arm	• As PF F1
PF F5 Scenario	• As PF F1 plus • Relative dose intensity calculations use median relative dose intensity from BEACON (rather than mean)	• As PF F1
PF F6 Scenario	• As PF F1 plus • Drug wastage for intravenous vials assumed in 10% of patients	• As PF F1

Abbreviations: F, FOLFIRI; PF, Pierre Fabre.

The curve fits for the May 2020 BEACON overall survival data are described in ***5.a.1 Response***. All scenarios in Table 4 are self-explanatory, except for scenarios PF F3 and PF F4. In these two scenarios, the company followed the same methods as the ERG in terms of only using survival data post 2.8 months to inform the parametric modelling. However, in contrast to the ERG who used the August 2019 survival dataset, we used all available data from the May 2020 updated survival. The raw Kaplan-Meier data were used for the first three months; for the cycles after three months, the parametric models generated using survival data post 2.8 months were used. The survival probabilities beyond three months were then multiplied by the probability of having survived up to 2.8 months.

The selection of parametric models followed the same logic as was used in the original company submission. Separate parametric models were fit to the survival data for the encorafenib/cetuximab and control arms from BEACON (omitting all data points ≤2.8 months). The parametric model form with the lowest average AIC was then selected for use in the model (Table 5). It should be noted that there is little difference between the mean AICs presented for the generalised gamma, Gompertz, log-logistic and lognormal models. The log-logistic had the lowest AIC by a small margin and was selected for the analysis. The exponential model, which was selected by the ERG to model the August 2019 data, was the poorest-fitting model to the encorafenib/cetuximab data. The exponential model also fit poorly to the control arm dataset, as did the Weibull model.

In scenario PF F3 the encorafenib/cetuximab data was used in the model, as the control arm curves were generated via modification of the encorafenib/cetuximab curve with a hazard ratio derived from the indirect treatment comparison (as per our original base-case). Scenario PF F4 used both the encorafenib/cetuximab and control arm data, providing an alternate estimate for the outcomes data for the FOLFIRI comparator.

Table 5: AICs for the parametric models fit to BEACON OS data >2.8 months

Model	Encorafenib with cetuximab	Control	Mean
Exponential	1033.00	878.82	955.912
Generalised gamma	1027.42	874.33	950.873
Gompertz	1025.19	874.89	950.040
Log-logistic	1025.38	873.81	949.598
Lognormal	1028.40	873.45	950.923
Weibull	1028.97	879.02	953.996

Abbreviations: AIC, Akaike information criterion

Results

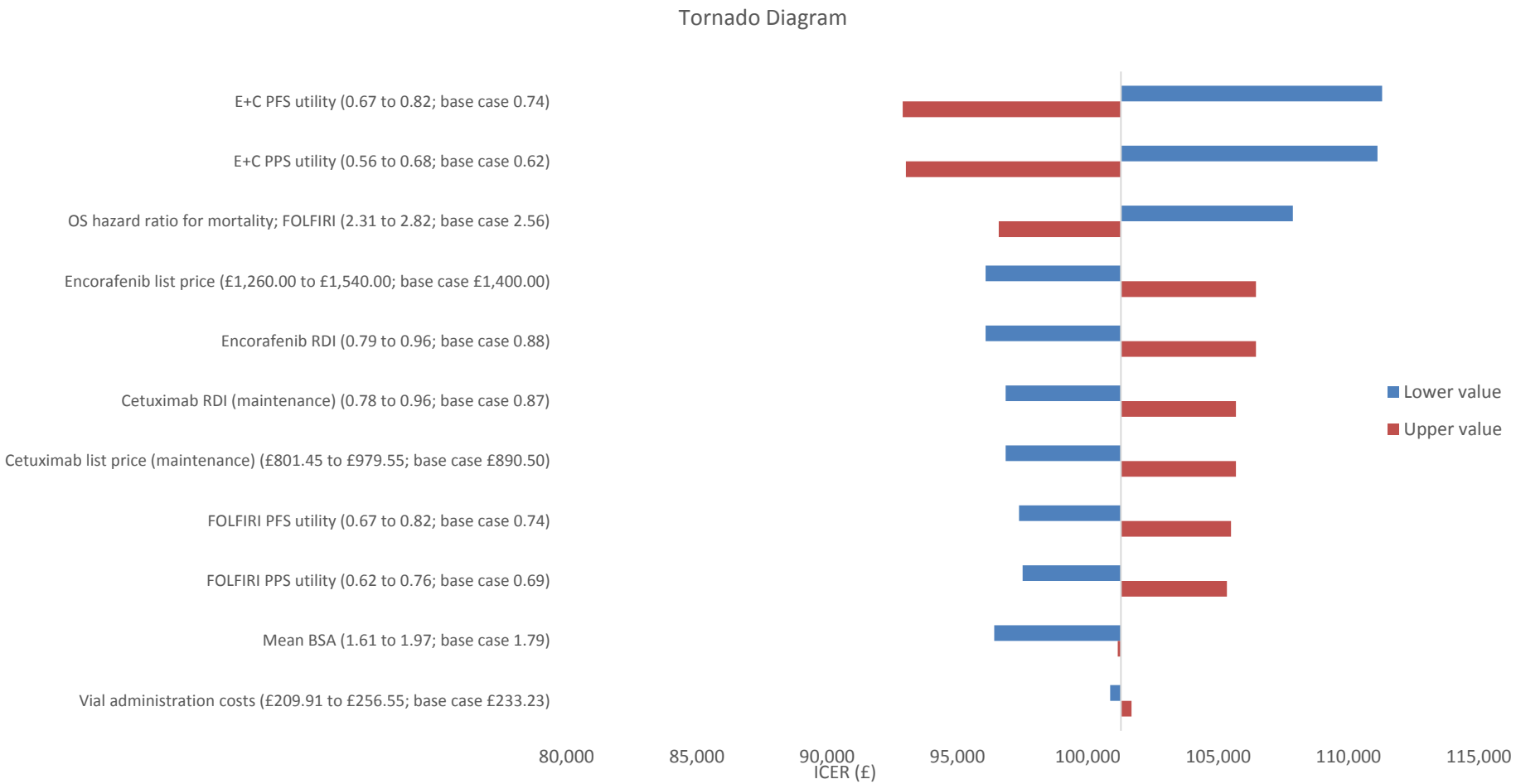
Table 6: Pairwise results versus FOLFIRI

Analysis	E+C cost (£)	F cost (£)	E+C LYG	F LYG	E+C QALYs	F QALYs	Δ cost (£)	Δ LYG	Δ QALYs	ICER (all drug prices at list)
Company submission base case (using list prices)	£68,809	£12,391	1.362	0.586	0.917	0.402	£56,418	0.775	0.516	£109,410
PF F1 Revised base-case	£67,466	£12,387	1.448	0.600	0.973	0.429	£55,079	0.848	0.544	£101,198
PF F2 Scenario	£67,466	£13,547	1.448	0.960	0.973	0.677	£53,919	0.488	0.296	£181,925
PF F3 Scenario	£67,654	£12,481	1.645	0.605	1.092	0.432	£55,173	1.041	0.660	£83,567
PF F4 Scenario	£67,654	£13,665	1.645	1.005	1.092	0.707	£53,989	0.640	0.385	£140,228
PF F5 Scenario	£72,083	£12,407	1.448	0.600	0.973	0.429	£59,677	0.848	0.544	£109,645
PF F6 Scenario	£68,136	£12,404	1.448	0.600	0.973	0.429	£55,731	0.848	0.544	£102,397

Abbreviations: Δ, incremental; E+C, encorafenib with cetuximab; F, FOLFIRI; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PF, Pierre Fabre; QALY, quality-adjusted life year.

PF F1 revised base case: Deterministic results

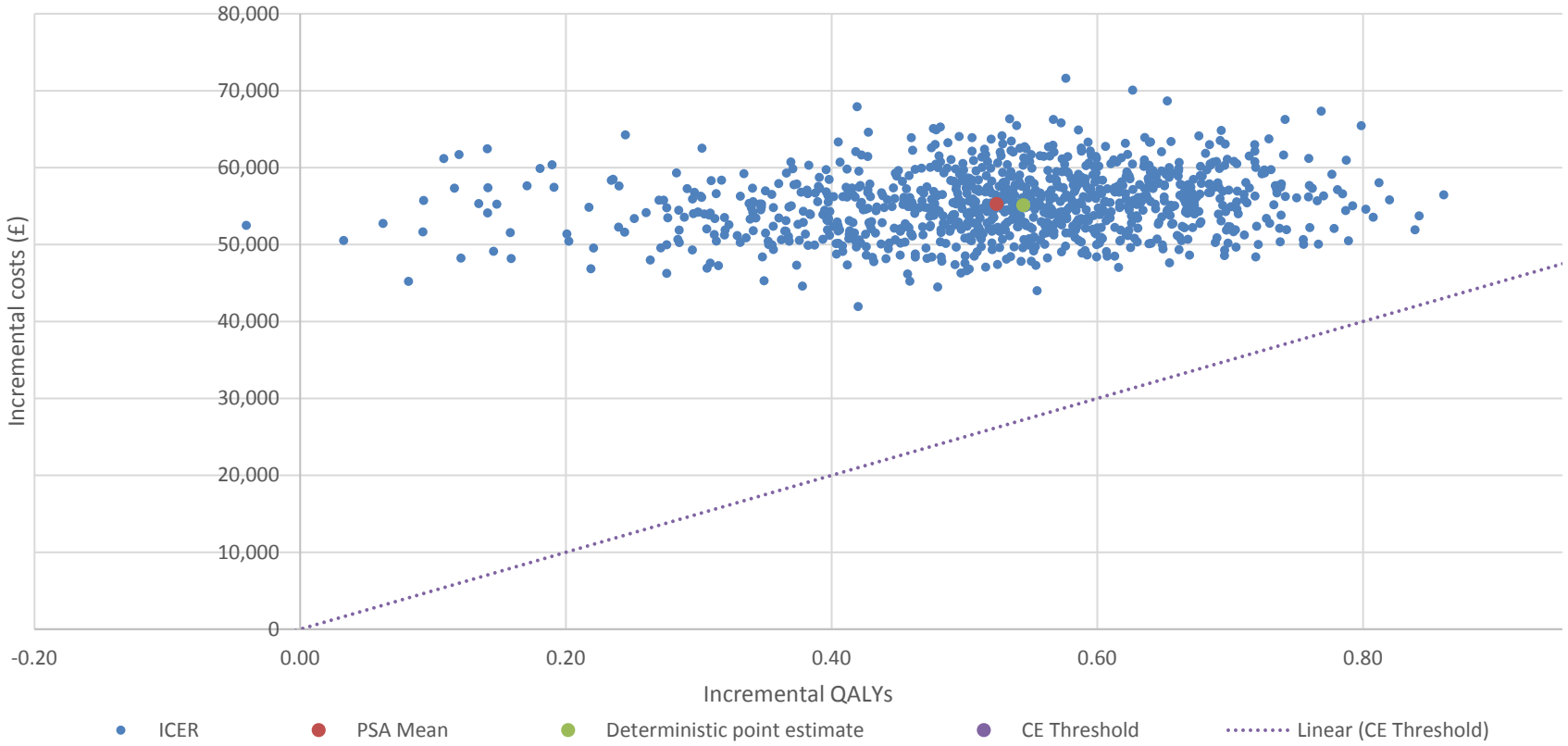
Figure 9: PF F1 revised base case: Tornado diagram versus FOLFIRI



Abbreviations: BSA, body surface area; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; RDI, relative dose intensity.

PF F1 revised base case: Probabilistic results

Figure 10: PF F1 revised base case: Cost-effectiveness frontier versus FOLFIRI



Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years.

Table 7: PF F1 revised base case: Probabilistic results versus FOLFIRI

Drug	Costs (SD)	LYG (SD)	QALYs (SD)	Δ cost (£)	Δ LYG	Δ QALYs	ICER (all drug prices at list)
FOLFIRI	£12,387 (£818)	0.632 (0.196)	0.452 (0.136)				
E+C	£67,640 (£4,167)	1.454 (0.111)	0.976 (0.070)	£55,253	0.82	0.52	£105,387

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gain; QALY, quality-adjusted life year; SD, standard deviation.

11.2 Response: Revised analyses versus trifluridine-tipiracil

Description of scenarios

Table 8: Key parameters for revised pairwise analyses versus trifluridine-tipiracil

Analysis	Key parameters/changes from company submission base case	Additional changes
Company submission base case	• Encorafenib with cetuximab: August 2019 overall survival & progression-free survival BEACON, fully parameterised log-logistic • Trifluridine-tipiracil: RECOURSE with Peeters 2015 BRAF adjustment	• N/A
PF TT1 Revised base-case	• Encorafenib with cetuximab: May 2020 overall survival & progression-free survival BEACON, fully parameterised log-logistic • Trifluridine-tipiracil: RECOURSE with Peeters 2015 BRAF adjustment	• TT utility values (average of encorafenib with cetuximab and FOLFIRI with cetuximab from BEACON) • Cetuximab dosing (500 mg/m^2 every 2 weeks, no initiation dose) • Relative dose intensity correction • Drug list prices
PF TT2 Scenario	• As PF TT1 plus • Trifluridine-tipiracil: RECOURSE with Safaee Ardekani 2012 BRAF adjustment	• As PF TT1
PF TT3 Scenario	• As PF TT1 plus • Encorafenib with cetuximab: May 2020 overall survival BEACON, use of KM curves to 2.8 months, followed by parameterised extrapolation (log-logistic) (progression-free survival remains as fully parametric as per base case)	• As PF TT1
PF TT4 Scenario	• Encorafenib with cetuximab: May 2020 overall survival & progression-free survival BEACON, pts with 2 prior treatments, fully parameterised log-logistic • RECOURSE overall survival & progression-free survival, pts with 2 prior treatments, with Peeters 2015 BRAF adjustment	• As PF TT1

Abbreviations: PF, Pierre Fabre; TT, trifluridine-tipiracil.

Results

Table 9: Pairwise results versus trifluridine-tipiracil

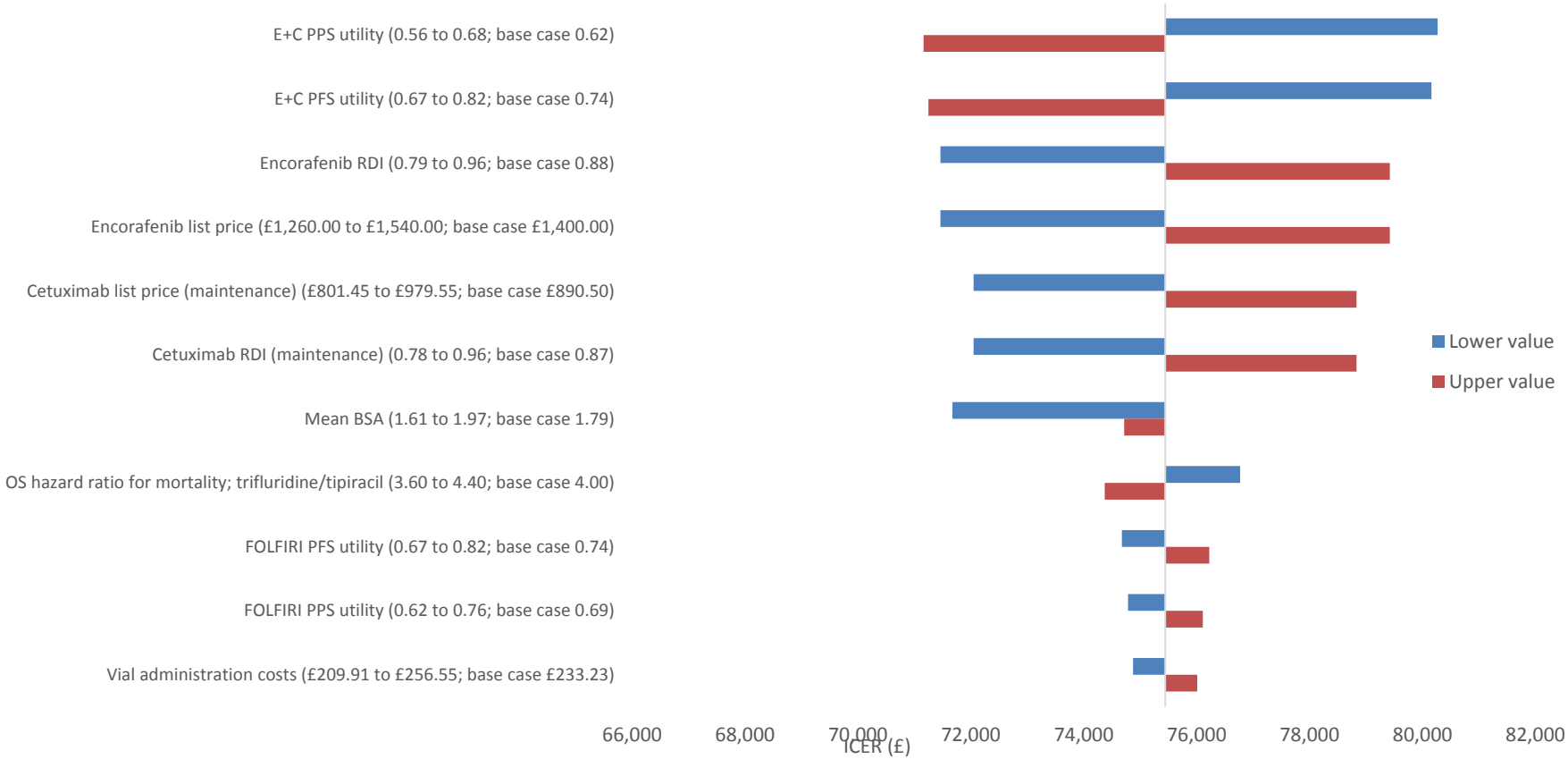
Analysis	E+C cost (£)	TT cost (£)	E+C LYG	TT LYG	E+C QALYs	TT QALYs	Δ cost (£)	Δ LYG	Δ QALYs	ICER (all drug prices at list)
Company submission base case (using list prices)	£68,809	£14,782	1.362	0.376	0.917	0.258	£54,027	0.986	0.659	£81,949
PF TT1 Revised base-case	£67,466	£14,782	1.448	0.376	0.973	0.264	£52,684	1.071	0.709	£74,296
PF TT2 Scenario	£67,466	£15,943	1.448	0.511	0.973	0.355	£51,523	0.937	0.618	£83,365
PF TT3 Scenario	£67,654	£14,782	1.645	0.376	1.092	0.264	£52,872	1.269	0.828	£63,833
PF TT4 Scenario	£63,349	£14,383	1.491	0.319	0.993	0.225	£48,966	1.172	0.767	£63,810

Abbreviations: Δ, incremental; E+C, encorafenib with cetuximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PF, Pierre Fabre; QALY, quality-adjusted life year; TT, trifluridine-tipiracil.

PF TT1 revised base case: Deterministic results

Please note that the below tornado diagram contains utility values for FOLFIRI PFS and PPS utility values; this is not an error. The utility values for trifluridine-tipiracil are generated as averages of the FOLFIRI and Enco with cetuximab utilities.

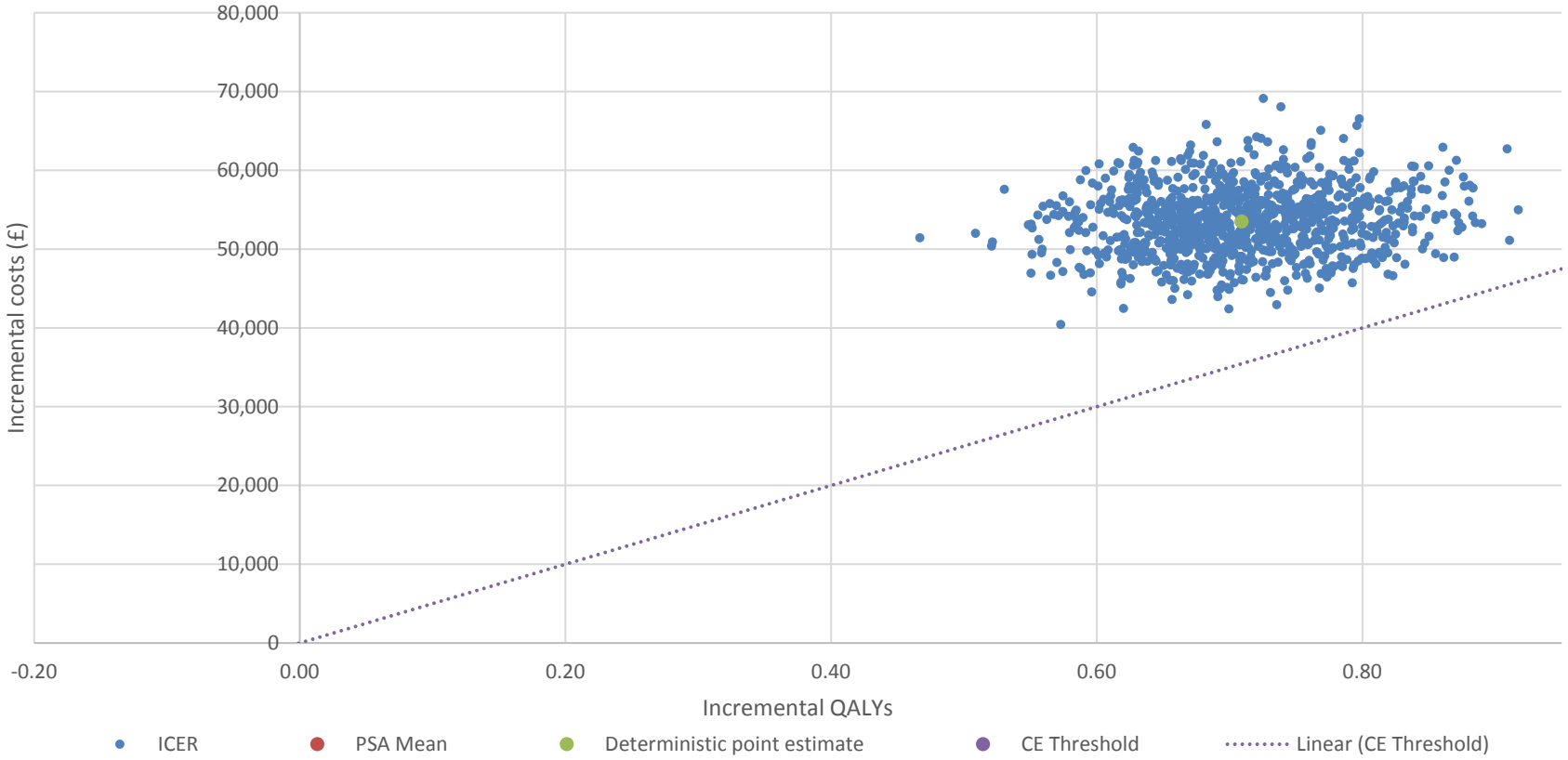
Figure 11: PF TT1 revised base case: Tornado diagram versus trifluridine-tipiracil



Abbreviations: BSA, body surface area; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; RDI, relative dose intensity.

PF TT1 revised base case: Probabilistic results

Figure 12: PF TT1 revised base case: Cost-effectiveness frontier versus trifluridine-tipiracil



Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years.

Table 10: PF TT1 revised base case: Probabilistic results versus trifluridine-tipiracil

Drug	Costs (SD)	LYG (SD)	QALYs (SD)	Δ cost (£)	Δ LYG	Δ QALYs	ICER (all drug prices at list)
Trifluridine-tipiracil	£14,152 (£467)	0.381 (0.032)	0.267 (0.021)				
E+C	£67,640 (£4,167)	1.454 (0.111)	0.976 (0.070)	£53,488	1.07	0.71	£75,414

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life year gain; QALY, quality-adjusted life year; SD, standard deviation.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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 questions below. You do not have to answer every question. 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 summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5:00pm, 13 July 2020**

Thank you for your time.

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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	[redacted] [redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Bowel Cancer UK in collaboration with Medical Advisory Board Members:** [redacted] [redacted] [redacted] xx[redacted]
Disclosure	**Nil**

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement

Issue 1: Treatment pathway	
Where would encorafenib plus cetuximab likely be used in NHS clinical practice? Is 2nd line the only relevant position for the committee to consider in their decision making?	**Second line most frequently, but third line is appropriate in patients who have progressed on second-line chemotherapy, have a performance status (PS) of 0-1 and who have not previously had the opportunity to access Encorafenib plus Cetuximab.**
Is single agent irinotecan an established 2nd line treatment for people with BRAF V600E mutation-positive metastatic colorectal cancer?	**Yes, though less frequently used than the FOLFIRI combination of bolus/infusional 5-FU, folinic acid and irinotecan. With increased DPYD gene testing, up to 10% of patients will not be appropriate for a fluoropyrimidine in this setting due to DPD deficiency and single agent irinotecan is the appropriate 2nd line chemotherapy.**
Is best supportive care a relevant comparator for people with previously treated BRAF V600E mutation-positive metastatic colorectal cancer?	**No, this combination should be used ahead of therapies such as Lonsurf *(*trifluridine-tipiracil*).***
Where in the treatment pathway is trifluridine-tipiracil used? Is trifluridine-tipiracil a relevant comparator for encorafenib plus cetuximab?	**Trifluridine/tipracil is used as third line therapy after failure of oxaliplatin and irinotecan based therapies in first and second line. Whilst we would recommend Encorafenib and Cetuximab in the second line setting, 3rd line remains a viable and appropriate option for this combination as above.**
Issue 2: Extrapolation of overall survival	
Does having a larger proportion of refractory patients in the RECOURSE trial have an impact on survival outcomes when compared to the BEACON CRC trial?	**Yes, separate trials are rarely directly comparable as the patients within separate trials are not randomised against one another and thus bias will exist. More heavily pre-treated patients will have worse survival and response outcomes, in general. In addition,**

	Encorafenib and Cetuximab are appropriate therapies only for the 8-10% of patients with metastatic CRC whose tumours have V600E activating mutations in the BRAF gene.
Are outcomes of patients who have previously received EGFR inhibitors expected to differ from patients who are EGFR naïve? Does this differ by place in the treatment pathway?	**This has no relevance here as a comparator, as guidelines, though not licensed would routinely recommend avoidance of EGFR inhibitors alone or in combination with chemotherapy in tumours with a BRAF mutation. There is no molecular or other selection marker for Trifluridine/tipracil.**
Are the RECOURSE data used in the economic modelling robust and appropriate for decision making?	**Yes, we would support these.**
Issue 3: Indirect treatment comparison	
Is FOLFIRI equivalent to irinotecan in terms of clinical effectiveness? Would efficacy of either treatment be different in the BRAF-mutant population compared to wildtype?	**Yes, in terms of efficacy for the purposes of this evaluation, though toxicity profiles do differ and the preferred option in the UK and internationally would be FOLFIRI, with a select group of patients receiving irinotecan as a single agent. Both FOLFIRI and irinotecan monotherapy have lower response rates, progression free survival (PFS) and overall survival (OS) in patients with BRAF V600E mutations than in those whose tumours are BRAF wild type.**
Is cetuximab equivalent to panitumumab in terms of clinical effectiveness?	**Yes, effectiveness is equivalent as indicated in head to head trials (e.g. ASPECCT[i]) in the last line setting where panitumumab is non-inferior to cetuximab. It is extrapolated that this is the scenario in the first line combination setting. Some groups argue that the chemotherapy backbone (oxaliplatin or irinotecan) has differential efficacy when compared with panitumumab or cetuximab. Advocates for these retrospective overviews would link cetuximab with irinotecan +/- 5-FU and panitumumab with oxaliplatin + 5-FU in the first line setting.**

Issue 4: BEACON CRC trial as a proxy for estimating relative effectiveness	
Is cetuximab clinically effective for people with previously treated BRAF V600E mutation-positive metastatic colorectal cancer?	**It has been shown to have no meaningful activity in retrospective analyses in BRAF V600E mutant metastatic colorectal cancer.**
Issue 5a: Modelling overall survival for BEACON CRC Encorafenib plus cetuximab data	
For people who have had previous treatment for metastatic BRAF-V600E mutation positive colorectal cancer, and received Encorafenib plus Cetuximab what proportion would you expect to survive to 3 and 5 years?	**Real world data is always challenging to extract from trial based cohorts, who generally have better outcomes. It can be estimated:** **3yr OS = 20%** **5Yr OS= ~3%**
How informative is the ERG's analysis regarding the extrapolation of overall survival?	**Reasonably informative.**
Issue 5b: Modelling overall survival for the comparator arm	
For people who have had previous treatment for metastatic BRAF-V600E mutation positive colorectal cancer, and receive current standard of care as 2nd line what proportion would you expect to survive to 3 and 5 years respectively?	**3% and 0% respectively.**
Based on data presented is the company's approach to modelling overall survival appropriate?	**Yes.**
Issue 6: Modelling progression free survival	

What proportion of patients would be expected to remain progression free at 3 years after having had encorafenib plus cetuximab?	**0%.**
Is the ERG's approach to modelling progression free survival appropriate?	**Yes.**
Issue 7: Modelling time to treatment discontinuation	
Is it appropriate to assume that time to treatment discontinuation is the same as progression free survival for encorafenib plus cetuximab and the relevant comparators?	**No - patients will stop therapy due to toxicities, intercurrent unrelated illness, or their need for treatment holidays and guidance should accept the patient need for this to occur, and not to be limited by an artificial time frame.**
Issue 8: Utility values	
Are the utility values included in the company model appropriate?	
Issue 9: Cost uncertainties in the analysis	
What is the correct dosage of cetuximab in clinical practice?	**500mg/m2 every 2 weeks (although the licensed dose is 400mg/m2 in the first week and 250 mg/m2 every week thereafter. The every 2 week dosing is supported by pharmacokinetic studies, comparative clinical trials (albeit with small sample sizes) and real world evidence.**
Do the differences in the relative dose intensities of cetuximab impact on the robustness of the cost-effectiveness estimates?	**No.**
Is the assumption of no drug wastage reasonable?	**Cetuximab is sold using a vial based approach therefore drug wastage cannot be excluded, and for greater accuracy should be incorporated.**
Issue 10: End of life criteria	

Does the evidence support that encorafenib plus cetuximab extends life by 3 months or more compared with current practice?	**Yes.**
Under standard care, is the life expectancy of adults with previously treated BRAF-V600E mutation positive metastatic colorectal cancer less than 24 months?	**Yes.**

[i] https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70118-4/fulltext

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer

ERG critique of company technical engagement response

Produced by *Warwick Evidence*

Date completed *28 July 2020*

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC).

1 ERG comments upon company technical engagement (TE) response

The ERG provides comments by issue. It should be noted that the ERG had very limited time to comment upon the company response to TE and did not have access to many of the new data that the company presents results for. This very much limits the critique of the ERG and the analyses that the ERG can sensibly present.

1.1 Issue 1: Possible effect of encorafenib upon the treatment pathway

The company states that those receiving 1st line FOLFOXIRI will currently receive 2nd line trifluridine + tipiracil. The company goes on to state that if 2nd line encorafenib is not cost effective against 2nd line FOLFIRI, it should be assessed against 2nd line trifluridine + tipiracil.

If encorafenib + cetuximab is approved at 2nd line against trifluridine + tipiracil in effect this approves the treatment sequence of 1st line FOLFOXIRI followed by 2nd line encorafenib + cetuximab. It is not possible to restrict use of 2nd line encorafenib + cetuximab to only those who would currently receive 2nd line trifluridine + tipiracil. Clinicians want to use encorafenib + cetuximab at 2nd line for their patients. ERG expert opinion suggests that under such a restriction patients who are currently treated with 1st line FOLFOX followed by 2nd line FOLFIRI would in future tend to be treated with 1st line FOLFOXIRI (if it is expected that they can tolerate the treatment regimen) followed by 2nd line encorafenib + cetuximab. Since the use of FOLFOXIRI for 1st line currently applies to a minority of patients, the main comparator for 2nd line encorafenib + cetuximab is 2nd line FOLFIRI. When this is coupled with the major concerns around the naïve comparison with trifluridine + tipiracil, the ERG questions the relevance to decision making of the cost effectiveness estimates for encorafenib + cetuximab compared to trifluridine + tipiracil.

1.2 Issue 2: Trifluridine + tipiracil effectiveness and subgroups

The company February 2020 submission gave no consideration to the comparator arm of RECOURSE and only provided a naive comparison of the RECOURSE trifluridine + tipiracil arm with the BEACON encorafenib dual therapy arm. The hazard ratios cited in the company TE response are not relevant to this. What is relevant to this naïve comparison is whether patients with more prior treatment tend to have longer remaining OS when treated with trifluridine + tipiracil than patients with fewer prior treatments. The company argues that confounding variables may differ between the RECOURSE trial prior treatment subgroups. This strongly argues for a consideration of the confounding variables; if possible a formal analysis of the RECOURSE data, but at a minimum a comparison of these across RECOURSE and BEACON, before any naïve comparison can be undertaken. The possibility of confounding variables in general within RECOURSE compared to BEACON also demands that the parameterised curves be placed in context before any subgroup analyses are undertaken.

The company base case log-logistic curves are presented below, with the RECOURSE trial curve being conditioned by the HR of 4.00 to arrive at the trifluridine + tipiracil curve.

Figure 1. Company OS curves: BEACON vs RECOURSE

The main point to note is that despite RECOURSE not being restricted to BRAF V600E mutation and being mainly wild type, its OS curve is considerably worse than the OS curve for encorafenib which is restricted to BRAF V600E mutation. Indeed, the RECOURSE trial wild type OS curve is virtually the same as the BEACON trial BRAF V600E mutant control arm OS curve. Given the serious effect that BRAF V600E mutation is mooted to have upon OS, the ERG finds this surprising. It may call into question the reasonableness of the naïve comparison and the application of the BRAF V600E hazard ratio to the RECOURSE trial curve.

These concerns are amplified when the 2-prior subgroup analyses are examined, the figure below amending the encorafenib curve and the RECOURSE curve to be the company 2-prior analyses. A 2-prior analysis is not presented for the BEACON control arm, and this remains the all patients curve.

Figure 2. Company OS curves: BEACON vs RECOURSE: 2 prior subgroup

It is possible that other prognostic factors account for the overall poor survival in the RECOURSE trial. The distribution of these prognostic factors is likely to vary not only between subgroups defined by the number of prior therapies within the trials but also between the trials. The company TE response alludes to some of the prognostic factors that might be associated with apparently better survival for patients who had received more lines of prior treatment in the RECOURSE trial, "*such as low tumour burden, indolent disease, and absence of liver metastases*". It certainly seems possible that the patients entering RECOURSE may have differed considerably from those entering BEACON, for example time since initial diagnosis and types and nature of prior and concurrent treatments received, and not just in their BRAF V600E status. Details for these prognostic factors are not available to allow appropriate assessment of the comparison between the subgroups from the two trials, for which ERG also wish to emphasise its post hoc nature.

In the light of the above the ERG queries whether it is reasonable to apply the curves estimated from the RECOURSE trial, and if these are to be used whether it is reasonable to apply a hazard ratio to them. Given the above, the ERG preference is to use the BEACON control arm curves as the best proxy for the curves that would have resulted has trifluridine + tipiracil been used among the BEACON patient population.

1.3 Issue 2.3: BRAF V600E mutant vs wild type: application of hazard ratios

In addition to the estimated hazard ratio (HR) for overall survival (OS) of 4.00 from Peeters 2015 for patients with BRAF V600E mutation vs wild type used in the company's base case, the company has also identified a meta-analysis (Safaee Ardekani et al. 2012) that provides an alternative estimate of the hazard ratio of 2.24. This meta-analysis included 26 studies of colorectal cancers (CRC) at various stages of disease (i.e. both metastatic and earlier stages) from around the world and showed substantial heterogeneity (I^2 >70%) in the estimated hazard ratios. Among these studies, the ERG identified the MRC FOCUS trial (Richman et al. 2009) being one of the largest studies conducted in the UK in the setting of advanced CRC to provide a further plausible HR estimates for consideration. The study reported an estimated HR for BRAF V600E mutant vs wild type of 1.82 (1.36 to 2.43) for OS and of 1.14 (0.86 to 1.52) for progression free survival (PFS).

The OS for trifluridine + tipiracil that is modelled applying the company base case HR of 4.00 of Peeters et al can be compared with that modelled using the meta-analysis HR of 2.24 of Safaee Ardekani et al and the HR of 1.82 of the FOCUS trial, these hazard ratios being applied to the parameterised RECOURSE log-logistic curve of the company base case. The BEACON control arm and encorafenib arm log-logistic OS values are also presented for ease of reference.

Table 1. Modelled trifluridine + tipiracil OS by hazard ratio applied

	T&T			BEACON	
OS proportions	HR=4.00	HR=2.24	HR=1.82	CTRL	ENCO+c
3 months	[redacted]				
6 months					
1 year					
2 year					
3 year					
5 year					
10 year					

For the HR of 4.00 the median survival for trifluridine + tipiracil is little more than 3 months, and effectively all have died within the 1st year. This begs the question of what the implied median OS would be for BRAF V600E patients in the comparator arm of RECOURSE; vanishingly short if the company method is applied. For the HR of 2.24 the median survival is a little more than 4 months but still only [redacted] remain alive at the end of the 1st year compared with 43% for encorafenib dual therapy. The FOCUS trial HR sees [redacted] surviving to 1 year. The ERG will provide scenario analyses which apply the various hazard ratios to the RECOURSE trial curves estimated by the company.

Note that a proportion of patients in RECOURSE will have been BRAF V600E. It is not clear whether the various HRs need further adjustment for this, as they were derived by comparing the survival for patients with BRAF mutation vs patients *without* BRAF mutation.

1.4 Issue 3: Equivalence of FOLFIRI and irinotecan

The company asserts that the BEACON FOLFIRI OS KM curve and irinotecan OS KM curve are broadly aligned, and notes that BEACON was not powered to investigate a difference and by implication that these subgroups should not be examined individually. The ERG provides these below for ease of reference.

Figure 3. BEACON control arm split by treatment subgroup

The company suggestion that a lack of power and a lack of difference between the FOLFIRI + cetuximab subgroup and the irinotecan + cetuximab subgroup means that these subgroup should not be explored also needs to be read alongside the company presenting prior treatment subgroup analyses of the BEACON trial data in its comparison with trifluridine + tipiracil. The ERG presents these below for ease of reference.

Figure 4. BEACON encorafenib arm split by number of prior treatments

1.5 Issue 4: Hazard ratio for adding cetuximab to FOLFIRI

The ERG has nothing to add to its critique of the main ERG report. The ERG maintains that the most appropriate base case assumption is to not apply the company ITC HR for cetuximab use to the BEACON control arm curves.

1.6 Issue 5: New data cut and revised fitting of curves

The data seems to be an unplanned data cut. It also appears to exhibit the same peculiar evolution of the hazard in the encorafenib dual therapy arm. The ERG has not had access to this data. This and time constraints limit the ERG critique. The ERG reiterates that smooth parameterised curves did not fit the planned BEACON OS KM data cut very well, hence its preference for the ERG piecewise fits.

The company has provided very limited information about its fitting of piecewise curves to the encorafenib dual therapy arm new OS KM data, other than the AIC as tabled below. It has not provided the parameter estimates underlying each of the curves, and only provides as pure number the piecewise log-logistic and what appears to be the piecewise exponential for the encorafenib dual therapy arm. The ERG does not have access to the new BEACON KM OS data and as a consequence cannot meaningfully interrogate what little the company has supplied.

Table 2. Company piecewise curves' AIC

Model	Encorafenib + C	Control	Mean
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

The company's original submission presented both the AIC and the BIC of the relevant curves, as is standard. It is a concern that the company only presents the AIC in its response to technical engagement.

The company has estimated piecewise curves for both the encorafenib dual therapy arm and the control arm of BEACON. It does not present any of the control arm curves, or use any of them in the model. But it does use the AIC of the control arm curves to suggest that the lowest AIC is for the log-logistic. If the company thinks that the control arm curves are relevant they should be presented, if not it is invalid to use the control arm information criteria to justify the selection of the encorafenib curve.

For the encorafenib arm the log-logistic is not the "lowest AIC by a small margin". There is little to choose between any of the encorafenib curves on the basis of their AIC. A more detailed presentation is required, including a presentation of the remaining curves and the curves of the control arm before it can be decided which if any of the curves are a sensible choice.

The company implementation of the piecewise log-logistic is peculiar in that up to cycle 196 of the model it is inputted as pure number but from cycle 197 it applies the parameters of the non-piecewise log-logistic. This results in a step in the function as shown below.

Figure 5. Company revised encorafenib OS curves, including piecewise curves

Up to cycle 196 the piecewise log-logistic lies everywhere above the log-logistic. The company has arbitrarily restricted the piecewise log-logistic to only apply for a period of time, possibly due to it modelling infeasible proportions remaining alive in the long term. At the 10 year time horizon the piecewise log-logistic curve estimates that [redacted] of encorafenib patients remain alive.

Perhaps surprisingly given the piecewise log-logistic fit, what appears to be the piecewise exponential curve lies a little above the exponential curve for the first year but then falls below it.

There is little to choose between the piecewise curves in terms of information criteria. The above underlines the need to consider the piecewise fitting of curves in greater detail before deciding upon which, if any, should be used for modelling purposes. Given this, the ERG thinks that the company piecewise log-logistic should not be used for modelling purposes. Either that or the 10 year time horizon is insufficient for modelling purposes.

The original ERG report outlined the poorness of fit of the smooth parameterised curves, opting instead for the ERG piecewise fits to the original data cut. Given this, the concerns outlined above about the company log-logistic fit to the new data cut and that the ERG does not have access to the new data cut, for its exploratory base case the ERG retains its piecewise fits to the original data cut.

1.7 Issue 6: Long term PFS

The ERG has not been given access to the new Kaplan Meier data cut of the PFS. The ERG questions whether too much attention should be paid to the extreme right hand tail estimate of [redacted] that the company emphasises due to only [redacted]; i.e. less than 1%, of patients remain at risk in the encorafenib dual therapy arm.

1.8 Issue 7: PFS and Time on treatment

The company reasserts its original argument.

The company asserts that for analyses using the company ITC a time to treatment discontinuation curve would not be available for the comparator arm. The ERG position is that the base case comparison with FOLFIRI should not apply the company ITC, so for this analysis this argument does not apply.

The company analyses seem counterintuitive to the ERG, suggesting that using the time to treatment discontinuation (TTD) curve rather than PFS curve results in a lower total cost in the encorafenib + cetuximab arm.

The unadjusted Kaplan Meier data suggests that the TTD curve typically lies above the PFS curve.

Figure 6. Encorafenib PFS and TTD curves

When withdrawal of consent and receipt of subsequent treatment are treated consistently as censoring events for both the PFS and TTD curve (see section 4.3.3.8 of the ERG report), the TTD curve lies consistently above the PFS curve. The company does not address this in its response.

Figure 7. Encorafenib PFS and TTD curves: consistent treatment of censoring

The ERG finds it surprising that the company TTD costing results in lower encorafenib + cetuximab costs than does the company PFS costing. The ERG has not attempted to replicate the company curves.

1.9 Issue 9.1: Cetuximab initiation dose

The Cancer Drug Fund (CDF) accepts cetuximab use for "*The treatment of previously untreated metastatic colorectal cancer*" and specifies that "*Cetuximab will be given as a 2-weekly regimen at a dose of 500mg/m^2*". As a consequence it appears that cetuximab use in the NHS may conform to that specified by the CDF rather than that specified by the SmPC. The revised 1st cycle cetuximab cost has relatively little effect upon the ICERs.

Due to time constraints that ERG has not implemented this in its exploratory base cases. The effect is to lower the cost in the encorafenib + cetuximab arm by £411, and so improves the ICER by £411

divided by the net QALY gain. The ERG thinks that this in itself is unlikely to affect decision making, particularly once the cetuximab PAS is taken into account which reduces the cost savings.

1.10 Issue 9.2: Relative dose intensities (RDI)

The original company submission only applied RDI proportions to IV treatments and not to oral treatments. The ERG agrees with this as the oral formulations are pack based. If patients consume less than a full pack, a full pack is still prescribed. The ERG thinks it more likely that patients will be prescribed packs on a regular basis, rather than being prescribed more packs on the day when their current packs have run out.

The company does not engage with the argument that averaging across individual patient's RDIs will give too much weight to patients who remain on treatment for only a short period of time. The ERG thinks it likely that it was these patients who had very low RDIs. As shown below, the encorafenib RDI data is highly skewed. If an RDI is to be applied the ERG thinks that the median is likely to be a better estimate of the average that should be applied over the time horizon of the model for costing purposes.

Table 3. BEACON encorafenib RDI data

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

The ERG will supply scenario analyses that apply the median RDI to the encorafenib cost and the mean RDI to the encorafenib cost.

1.11 Issue 9.3: Cetuximab vial sharing

Non-vial sharing of cetuximab vials among 10% of patients is arbitrary. The company provides no justification for this 10% value. The ERG will supply a scenario of no vial sharing. This enables relatively simple interpolation for other vial sharing proportions; e.g. the ICER for 50% vial sharing will be midpoint between the base case ICER with 100% vial sharing and the scenario ICER with 0% vial sharing.

1.12 Issue 11: Company TE response cost effectiveness estimates

The ERG has tried to replicate the company TE analyses with the following results.

Table 4. Company TE estimates vs FOLFIRI: ICER

	Company	ERG
PF F1: Updated curves, FOLFIRI QoL, cetuximab dose, encorafenib mean RDI	£101,198	£101,381
PF F2: Using BEACON control arm as comparator	£181,925	£182,390
PF F3: Piecewise log-logistic encorafenib arm	£83,567	£83,702
PF F4: PF F2 and PF F3 combined	£140,228	£130,664
PF F5: Median RDI rather than mean	£109,645	£109,787
PF F6: 10% vial wastage	£102,397	£102,631

The ERG thinks that for decision making purposes the ERG replications for the comparison with FOLFIRI are sufficiently close to those of the company. The possible exception to this is PF F4. The discrepancy here is peculiar given that it is a combination of PF F2 and PF F3, the ERG replications of which are very close to those of the company. Since the ERG takes its modelling through to the cPAS appendix, the ERG asks that the company cross check the company's implementation of PF F4 and the ERG interpretation of this scenario analysis.

For the comparison with trifluridine + tipiracil the company cost effectiveness estimates and ERG attempts to replicate are as follows.

Table 5. Company TE estimates vs Trifluridine + tipiracil: ICER

	Company	ERG
PF F1: Updated curves, T&T QoL, cetuximab dose, encorafenib mean RDI	£74,296	£73,993
PF F2: Meta-analysis BRAFV600 HR	£83,365	£83,006
PF F3: Piecewise log-logistic encorafenib arm	£63,833	£63,568
PF F4: 2 prior parameterised curves	£63,810	£63,501

The ERG thinks that for decision making purposes the ERG replications for the comparison with trifluridine + tipiracil are sufficiently close to those of the company.

2 ERG analyses

The ERG provides an extended set of analyses for the comparison with FOLFIRI, and some exploratory analyses for the comparison with trifluridine + tipiracil.

2.1 ERG analyses: encorafenib + cetuximab compared to FOLFIRI

The ERG has not had access to the new data cut, thinks that the new company smooth parameterised curves are likely to be a poor fit to the data and is sceptical about the new company piecewise curves given to the highly selective company presentation of them. As a consequence, for its preferred exploratory base case the ERG retains its analysis of the main ERG report.

The ERG augments this with additional scenario analyses that apply the new company Weibull, log-logistic and piecewise fitted curves and explore applying an RDI to the encorafenib costs.

Note that due to time constraints the above does not take into account the company preferred cetuximab dosing during the 1st model cycle. This reduces costs in the encorafenib + cetuximab arm by £411 so improves the base case cost effectiveness estimates by £1,890 per QALY. But it should be borne in mind that this does not include the cetuximab PAS.

Table 6. Updated ERG estimates: encorafenib + cetuximab vs FOLFIRI: ICER

Analysis	ICER £/QALY
Base case	£242k
SA01a: ERG OS Weibull piecewise from 3 months	£227k
SA01b: ERG OS Gompertz piecewise from 3 months	£139k
SA01c: ERG OS Log-normal piecewise from 3 months	£202k
SA01d: ERG OS Log-logistic piecewise from 3 months	£201k
SA01e: ERG OS generalised gamma piecewise from 3 months	£206k
SA02a: ERG PFS exponential piecewise from 2 months	£245k
SA02b: ERG PFS Gompertz piecewise from 2 months	£258k
SA02c: ERG PFS Log-normal piecewise from 2 months	£280k
SA02d: ERG PFS Log-logistic piecewise from 2 months	£277k
SA02e: ERG PFS generalised gamma piecewise from 2 months	£254k
SA03: HRs applied to BEACON control arm to estimate FOLFIRI	£142k
SA04: HRs applied to BEACON encorafenib arm to estimate FOLFIRI	£149k

Table 6 (continued). Updated ERG estimates: encorafenib + cetuximab vs FOLFIRI: ICER

SA05a: Company Log-logistic curves for OS and PFS	£203k
SA05b: Company Weibull curves for OS and PFS	£216k
SA05c: Company piecewise log-logistic OS encorafenib	£116k
SA05d: Company piecewise exponential OS encorafenib	£210k
SA05e: Company piecewise log-logistic OS encorafenib + ITC HR	£92,933
SA05f: Company piecewise exponential OS encorafenib + ITC HR	£149k
SA06: Quality of life values not arm specific	£215k
SA07: TA405 PPS QoL value of 0.59	£215k
SA08a: 100% IV relative dose intensities	£251k
SA08b: BEACON mean IV relative dose intensities	£236k
SA08c: BEACON median encorafenib relative dose intensities	£238k
SA08d: BEACON mean encorafenib relative dose intensities	£226k
SA09: No vial sharing	£265k
SA10: Encorafenib + cetuximab PPS cost proportionate to time in PPS	£243k

2.2 ERG analyses: encorafenib + cetuximab compared to trifluridine + tipiracil

Due to the similarity of the company RECOURSE curves with those of the BEACON control arm, the ERG thinks that the naïve comparison and the application of BRAF V600E mutant vs wild type hazard ratios to the RECOIRSE trial data is flawed. The ERG prefers the starting point of assuming that if patients in the BEACON control arm had received trifluridine + tipiracil their experience would most closely mirror that of the control arm of BEACON. The ERG also presents scenario analyses which apply the various company RECOURSE parameterised curves, associating these with various hazard ratios.

Note that due to time constraints the analyses do not take into account the company preferred cetuximab dosing during the 1st model cycle. This reduces costs in the encorafenib + cetuximab arm by £411 so improves the base case cost effectiveness estimates by £1,762 per QALY.

Due to time constraints the ERG has not be able set up the model to run probabilistically for the comparison with trifluridine + tipiracil.

Table 7. Updated ERG estimates: encorafenib + cetuximab vs trifluridine + tipiracil: ICER

Analysis	ICER £/QALY
Base case	£199k
SA01a: Company log-logistic curves, Peeters BRAF HR	£82,970
SA01b: Company log-logistic curves, Safaee Ardekani BRAF HR	£93,307
SA01c: Company log-logistic curves, FOCUS BRAF HR	£97,731
SA01d: Company log-logistic curves, no BRAF HR	£167k
SA01e: Company Weibull curves, Peeters BRAF HR	£93,932
SA01f: Company Weibull curves, Safaee Ardekani BRAF HR	£109k
SA01g: Company Weibull curves, FOCUS BRAF HR	£117k
SA01h: Company Weibull curves, no BRAF HR	£256k
SA01i: Company 2-prior log-logistic curves, Peeters BRAF HR	£71,269
SA01j: Company 2-prior log-logistic curves, Safaee Ardekani BRAF HR	£78,491
SA01k: Company 2-prior log-logistic curves, FOCUS BRAF HR	£81,664
SA01l: Company 2—prior log-logistic curves, no BRAF HR	£128k
SA06: Quality of life values not arm specific	£188k
SA07: TA405 PPS QoL value of 0.59	£189k
SA08a: 100% IV relative dose intensities	£207k
SA08b: BEACON mean IV relative dose intensities	£193k
SA08c: BEACON median encorafenib relative dose intensities	£195k
SA08d: BEACON mean encorafenib relative dose intensities	£183k
SA09: No vial sharing	£220k
SA10: Encorafenib + cetuximab PPS cost proportionate to time in PPS	£200k

3 References

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