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

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

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Pierre Fabre**
   - **Company ACD response appendix**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. National Cancer Research Institute (NCRI) & Royal College of Physicians joint response
   b. Merck

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**
   - **Evidence Review Group additional information**

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
1	Consultee	Pierre Fabre	As requested, Pierre Fabre have provided additional analyses of the BEACON control arm. Please see full details in Addendum, Section 1, as agreed with NICE.	Thank you for your comment and for providing additional analyses of the BEACON CRC control arm to explore the assumption of equivalence between FOLFIRI and irinotecan. The committee considered the evidence as part of its decision making and concluded that irinotecan may not be equivalent to FOLFIRI (see FAD section 3.10).
2	Consultee	Pierre Fabre	As requested, Pierre Fabre have provided additional economic analyses for encorafenib/cetuximab versus FOLFIRI. Please see Addendum, Section 2.2, as agreed with NICE	Thank you for your comment and for providing additional analyses for encorafenib plus cetuximab compared with FOLFIRI. The committee consider the analyses as part of its decision making.
3	Consultee	Pierre Fabre	As requested, Pierre Fabre have provided additional economic analyses for encorafenib/cetuximab versus trifluridine-tipiracil. Please see Addendum, Section 2.3, as agreed with NICE	Thank you for your comment and for providing additional analyses for encorafenib plus cetuximab compared with trifluridine-tipiracil. The committee consider the analyses as part of its decision making.
4	Consultee	Pierre Fabre	As requested, Pierre Fabre have provided economic analyses for encorafenib/cetuximab versus BSC. Please see Addendum, Section 2.4, as agreed with NICE	Thank you for your comment and for providing additional analyses for encorafenib plus cetuximab compared with best supportive care. The committee considered comments received during consultation that patients eligible for best supportive care would generally not be fit enough to have active treatment and concluded that best supportive care is not a relevant comparator for encorafenib plus cetuximab (see FAD section 3.7).
5	Consultee	Pierre Fabre	As requested, Pierre Fabre have provided additional clinical data pertaining to the May 2020 data cut from the BEACON study. Please see Addendum, Section 3, as agreed with NICE	Thank you for your comment and for providing additional clinical data for the May 2020 data cut of the BEACON CRC trial. The ERG provided updated analyses using these data which the committee considered.
6	Consultee	Royal College of Physicians	I am commenting on this document on behalf of the RCP as Chair of the adjuvant and advanced NCRI sub group but also in my role as GI team lead for the West of Scotland and a PI on the BEACON and ANCHOR studies. I am writing as I am really disappointed by the initial response and hope there is still time to reconsider.	Thank you for your comment.
7	Consultee	Royal College of Physicians	As I understand from the ACD conclusions the biggest area of committee uncertainty relates to the effect of the comparative treatments. There are some	Thank you for your comment. The ERG provided analyses that attempted to adjust for the presence of

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			fundamental issues with using the BEACON study control arm as a proxy for FOLFIRI, and attempting to then decide re how it fits within colorectal pathways in the UK given that FOLFIRI Cetuximab is not a standard of care in the UK, but was mandated at the time by the FDA. I therefore support the approaches made to try and adjust for the impact of cetuximab when added to FOLFIRI, recognizing various scenarios exist for modelling what the actual control arm should have been and what effect the cetuximab may or may not have had.	cetuximab in the control arm of the BEACON CRC study, which the committee considered as part of its decision making (see FAD section 3.23).
8	Consultee	Royal College of Physicians	From personal experience and using the data from CRYSTAL I would estimate that cetuximab would add approximately six weeks to survival compared to FOLFIRI or irinotecan alone. We can see below that both BRAF mutant and wild type patients do gain benefit from cetuximab it's just that the prognostic aspect of being BRAF mutant means patients still do much less well overall.	Thank you for your comment. The committee considered that cetuximab likely benefits patients so BEACON CRC may underestimate the relative effect of encorafenib plus cetuximab compared with FOLFIRI (see FAD section 3.9).
9	Consultee	Royal College of Physicians	Furthermore, it should also be noted that whilst the BEACON control arm included clinician's choice of either FOLFIRI, or irinotecan (in addition to cetuximab) it is widely accepted that patients tolerate FOLFIRI significantly better than single agent irinotecan.	Thank you for your comment. The committee considered that irinotecan is associated with worse toxicity and potentially poorer outcomes than FOLFIRI and concluded that including a blended comparator in the estimates of clinical and cost effectiveness does not reflect the comparison with FOLFIRI (see FAD section 3.11).
10	Consultee	Royal College of Physicians	Most importantly, in a group of patients who could potentially have orphan status (<10% of colon patients) and for whom we have made no advances in several decades until this novel doublet, it would seem (given the paucity of comparative data) appropriate to conclude that cetuximab has played a part in the control arm and that therefore the gain for the patients in the experimental arm is actually likely to be more rather than less predicted. At this point I would also like to highlight the concept of "proportional survival" for patients who are approaching end of life. An additional 4 or 5 months when you were only given six to live in the first place is quite different to the same amount of additional time if your estimated survival is measured in years not a short amount of months.	Thank you for your comment. The committee considered that cetuximab likely benefits patients so BEACON CRC may underestimate the relative effect of encorafenib plus cetuximab compared with FOLFIRI (see FAD section 3.9). The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. The Committee concluded that encorafenib plus cetuximab fulfilled the end-of-life criteria.
11	Consultee	Royal College of Physicians	I would also like to highlight that this is actually a very small number of patients and any impact on the NHS budget overall should be fairly negligible – from my estimates it would only be 20 patients per year in Scotland and 200-300 patients per year across the whole of the UK. Whilst appreciating budget impact may be less relevant to NICE decision making, the relative unmet need and rarity of the BRAFV600E mutation should be taken into account.	"The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. The Committee does take account of how its advice may enable the more efficient use of available healthcare resources. In general, the Committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
				resources increases." (from Guide to the methods of technology appraisal 2013, section 6.2.14). A costing report and template will be available when the guidance is published.
12	Consultee	Royal College of Physicians	Finally, as the BEACON trial allowed second or third line patients to be enrolled if I understand correctly NICE are making the assumption that the novel doublet would be as useful to patients in the third line setting. Our own audit data of the WOSCAN population showed that very few patients are fit enough for second line treatment (well below 50%) and none made it to third line treatment. Lonsurf has been approved but most clinicians accept that it is predominantly useful in patients with 'slow burn' disease and is certainly not deemed to be equivalent to FOLFIRI. Nor would one ever consider BRAF mutant patients to have 'slow burn' disease (those who are not refractory at the outset, have non visceral metastases, and who have responded to prior oxaliplatin and irinotecan based treatments). I cannot think of any situation where a clinician would use lonsurf prior to irinotecan or oxaliplatin based lines of treatment. This is contrary to the encorafenib/ cetuximab doublet where in fact two thirds of the patients in the trial where second line – i.e. clinicians would recruit to the trial rather than use conventional second or third line treatments. The pivotal Lonsurf trial did not drill down to the response based on RAS or BRAF but my personal experience is that it is extremely unlikely that a BRAF mutant patient would respond to Lonsurf and I would never choose to use this first should the novel doublet be approved. Looking to the future it seems likely that immunotherapy will be more helpful for the subset of patients who are BRAF mutant and MSI unstable and I would estimate the numbers who would be treated with encorafenib and cetuximab would drop further.	Thank you for your comment. The committee considered encorafenib plus cetuximab within its marketing authorisation 'for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy' and concluded that it may be used after 1 or more previous lines of treatment in clinical practice (see FAD section 3.3).
13	Consultee	Royal College of Physicians	I would urge NICE to reconsider its provisional response given the current lack of effective treatment options available. This is a small group of patients, often young, who have never had a bespoke treatment for their sub type of cancer. The treatment is very well tolerated and also has less AE's which means in the context of the ongoing COVID scenario it's an extremely helpful option to have for patients. It also involves less chair time which is critical in the current era of social distancing and capacity and negates the need for a PICC line. This small sub group of patients do so much worse than all other colon patients – and worse than most other solid tumour patients presenting with stage IV disease. It is only with giving our best treatments as soon as possible i.e. first or second line that we can open up options for further studies and incremental gains in survival. I find it very difficult to contemplate that an approximately 50% gain in survival (5.9 to 9.3 months) for such a small number of patients (max 200) would not be approved. Likewise if it was approved for use in third line or beyond this would effectively mean no patients would live long enough to benefit from this treatment as in my own clinical experience only the minority of patients make it to second line and non to third line.	Thank you for your comment. The committee considered that there are currently no effective treatments for this type of colorectal cancer, and that encorafenib plus cetuximab represents a step change in treatment. It concluded that there is an unmet need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer and that encorafenib plus cetuximab is an innovative treatment (see FAD sections 3.1 and 3.33).
14	Commentator	MSD	In Section 3.11, the appraisal committee acknowledge there is limited evidence for people with BRAF V600E mutation-positive metastatic colorectal cancer and that	Thank you for your comment, the committee acknowledged the uncertainty in the clinical evidence

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			"Encorafenib plus cetuximab is the first colorectal cancer treatment that targets the BRAF V600E mutation". This confirms the clinicians opinion that there is "currently no effective treatments for this type of colorectal cancer and encorafenib plus cetuximab represents a step change in treatment" also highlighted by the patients experts that explained "their cancer responded quickly to triple therapy (encorafenib plus binimetinib and cetuximab) and this was life-changing, whereas they saw little to no response on previous treatment." NICE committees are frequently called upon to make judgements based on incomplete or confounding information as clinical trial design can't always reflect the local practice which is shaped not only by clinical outcomes but also the local reimbursement landscape. The difficulty in defining a robust comparator on this occasion is reflective of the limited options available for these patients rather than a lack of efficacy, which has been clearly demonstrated through the trial results, is in line with clinical opinion and has been accepted by the committee. The committee remit to consider proper use of financial resources is also supported through this appraisal as the patient population size is limited in scope, identifiable through testing and is around 10% of the existing 1L mCRC who are BRAF mutant (Source: IPSOS, EPIC) (circa 1290 patient). Clinical experts have also confirmed that the patient response is frequently quick and quantifiable, further limiting the possibility of extensive prescribing without benefit.	base and took this into account in its decision making (see FAD sections 3.8 to 3.11). "The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. The Committee does take account of how its advice may enable the more efficient use of available healthcare resources. In general, the Committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases." (from Guide to the methods of technology appraisal 2013, section 6.2.14). A costing report and template will be available when the guidance is published.
15	Commentator	MSD	In Section 3.13, the committee noted that the assumption of clinical equivalence between irinotecan + cetuximab and FOLFIRI + cetuximab was uncertain, despite the company submitting two randomized controlled trials which showed the two treatments did not differ statistically in OS and PFS for the second-line treatment of mCRC. This is supported by other studies (not in the company submission) which show irinotecan and FOLFIRI without cetuximab for the second-line treatment of mCRC do not differ statistically for OS or PFS (Clarke et al 2011, Graeven et al 2007).1,2 1. Clarke et al. Eur J Cancer. 2011 Aug;47(12):1826-36. doi: 10.1016/j.ejca.2011.04.024. 2. Graeven et al. Onkologie. 2007 Apr;30(4):169-74. doi: 10.1159/000099636.	Thank you for your comment. The committee considered additional analyses submitted by the company of the BEACON CRC control arm. It concluded that irinotecan may not be equivalent to FOLFIRI (see FAD section 3.10).

Summary of comments received from members of the public

Theme	NICE Response
Generalisability of the BEACON CRC trial to NHS clinical practice "Trials were based upon 60 year old patients, and discriminate against younger people with a better prognosis."	Clinical experts considered that the age of patients in BEACON CRC reflected the age of patients who would be seen in NHS practice with previously treated BRAF V600E mutation-positive colorectal cancer. The committee were aware that its recommendation applied to everyone included in the marketing authorisation for encorafenib plus cetuximab, which does not restrict the treatment to any age group. So, it did not consider this an equalities issue (see FAD section 3.37).
Analyses do not fully capture quality of life benefit "I feel that some of the data analysis and qualitative and quantitative methods miss capturing real life stories and evidence" "Quality and quantity of life have not been given enough weight."	The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. The Committee concluded that encorafenib plus cetuximab fulfilled the end-of-life criteria.
Company does not capture cost savings from other treatments "I would urge that you consider the cost of chemotherapy, hospital admittance, other therapies for patients as well"	Cost of comparator chemotherapy regimens were taken into account in the economic model including administration and costs relating to peripherally inserted central catheter (PICC) line clearance for people having FOLFIRI. Health state costs in the model accounted for hospital attendance, medical oncologist outpatient consultations, home visits from community nurse specialists, nurse visits for PICC line flushing, GP home consultation. Cost of subsequent treatments including drug costs, dispensing and administration costs were also included.
Complete evidence base not explored "I don't think the most recent data sets have been taken into account" "A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs"	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission and ERG critique. It also carefully considered the comments received from C&Cs in response to the appraisal consultation document.
COVID-19 benefit "Cost of keeping the patient alive, not in chemotherapy and perhaps not being constantly admitted to hospital, taking up chemo spaces of those whose chemotherapy is shown to work must be of some benefit."	Cost of comparator chemotherapy regimens were taken into account in the economic model including administration and costs relating to peripherally inserted central catheter (PICC) line clearance for people having FOLFIRI. The committee noted that encorafenib with cetuximab was an innovative treatment.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments end of Friday 25 September 2020 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent	Pierre Fabre
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	Andrew Poll, Head of Market Access UK, Ireland & Nordics

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	As agreed with NICE, all analyses and associated narrative are provided in the separate addendum document. Details for each relevant section are provided below.
1	As requested, Pierre Fabre have provided additional analyses of the BEACON control arm. Please see full details in Addendum, Section 1, as agreed with NICE.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments end of Friday 25 September 2020 **email:** NICE DOCS

2	As requested, Pierre Fabre have provided additional economic analyses for encorafenib/cetuximab versus FOLFIRI. Please see Addendum, Section 2.2, as agreed with NICE
3	As requested, Pierre Fabre have provided additional economic analyses for encorafenib/cetuximab versus trifluridine-tipiracil. Please see Addendum, Section 2.3, as agreed with NICE
4	As requested, Pierre Fabre have provided economic analyses for encorafenib/cetuximab versus BSC. Please see Addendum, Section 2.4, as agreed with NICE
5	As requested, Pierre Fabre have provided additional clinical data pertaining to the May 2020 data cut from the BEACON study. Please see Addendum, Section 3, as agreed with NICE

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

Please return to: **NICE DOCS**

Encorafenib in dual or triple therapy for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [ID1598]
Consultation on the appraisal consultation document – company response addendum

1 Indirect treatment comparison

In response to ACD Section 3.34:

- The indirect treatment comparison: Analyses from the control arm of BEACON CRC split by treatment (FOLFIRI plus cetuximab or irinotecan plus cetuximab; see ACD section 3.13) including:
  - *adjustment for potential confounders*
  - *a log-rank test to assess the overall and progression-free survival.*

The BEACON trial was planned to compare the encorafenib/cetuximab arm with the control arm, comprising of investigator's choice of FOLFIRI/cetuximab and irinotecan/cetuximab, and was set up on the basis of equivalence between these two chemotherapy regimens; 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 either OS or PFS (1, 2).

The BEACON trial was ***not*** powered to detect differences between the encorafenib arm and the two chemotherapy regimens. As would have been anticipated the two chemotherapy treatments performed similarly, as shown by the non-statistically significant difference between the two OS curves (HR, 1.11; 95% CI [redacted]; stratified log rank one-sided p=[redacted], May 2020; stratified on ECOG performance status, source of cetuximab, and prior irinotecan use at randomisation) (3).

The use of one of the two pre-defined control chemotherapies was not randomised and was based on the clinical judgement of the investigator. In response to the Appraisal Committees request to explore any potential differences in the demographic and disease characteristics of patients who received the two regimens, we conducted a multivariate Cox analyses to take into account specific covariates identified as prognosis factors (Table 1). After adjusting on potential confounders, the impact of irinotecan/cetuximab and FOLFIRI/cetuximab on OS was still not statistically different (HR, [redacted]; 95% CI [redacted]) (3).

In conclusion, the additional data provides further support as to the equivalence of FOLFIRI/cetuximab and irinotecan/cetuximab, and remains consistent with expert clinical opinion.

Table 1: Stratified multivariate Cox regression model for OS, irinotecan/cetuximab vs FOLFIRI/cetuximab (FAS, May 2020 data cut)

	Hazard Ratio	95% CI	p-value (2-sided)
Full Cox Regression Model			
Irinotecan/cetux vs. FOLFIRI/cetux	[redacted]	[redacted]	[redacted]
Covariates			
Gender (Male vs. Female)	[redacted]	[redacted]	[redacted]
Age (<65 vs. >=65 years)	[redacted]	[redacted]	[redacted]
Removal of Primary Tumor (Complete Resection vs. Partial Resection/Unresected)	[redacted]	[redacted]	[redacted]
Baseline CRP (<=ULN vs. >ULN)	[redacted]	[redacted]	[redacted]
Side of Tumor			

	Hazard Ratio	95% CI	p-value (2-sided)
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]

CI, confidence interval; CRP, C-reactive protein; FAS, Full Analysis Set; MSI, microsatellite instability; OS, overall survival; SD, standard deviation; ULN, upper limit of normal.

2 New company economic analyses

We have provided several new economic analyses for encorafenib/cetuximab versus the following comparators, that we hope will assist the Committee in their decision making:

- versus FOLFIRI (Section 2.2).
- versus trifluridine-tipiracil (Section 2.3).
- versus best supportive care (BSC) (Section 2.4).

All economic analyses take account of the key points described in Section 2.1. These reflect specific preferences highlighted by the Appraisal Committee, as outlined in ACD section 3.34, as well as additional assumptions for some parameters/comparisons where a recommendation from the Committee was not provided.

2.1 Key points for new analyses

- BEACON May 2020 data cut for OS, PFS and, where applicable, TTD.
- OS from BEACON:
  - Fitted piecewise (Kaplan-Meier to 2.8 months, then parametric).
- OS from RECOURSE (trifluridine-tipiracil) and Kim 2018 (BSC):
  - Fitted fully parametric from time zero given that the assumption of piecewise from 2.8 months would not necessarily hold for data from other trials, a fully parametric approach was taken.
- PFS from BEACON:
  - Kaplan-Meier data to end of trial, followed by drop to zero, as per ERG assumption.
  - For analyses in which the ITC is used for FOLFIRI, the ITC HR is applied to the encorafenib/cetuximab PFS Kaplan-Meier.
- PFS from RECOURSE (trifluridine-tipiracil) and Kim 2018 (BSC):
  - Fitted fully parametric from time zero, to which the BRAF-mutant adjustment HR is applied; in the absence of guidance from the Appraisal Committee on the preferred approach for comparator trials, a fully parametric approach was taken consistent with the approach used for RECOURSE in the original company submission.
- Time on treatment:
  - For analyses that utilise the BEACON control arm as a proxy for FOLFIRI effectiveness, time to treatment discontinuation was used, as per the Committee's preference. A fully parametric model is fitted from time zero and the best fitting curve, based on lowest mean AIC/BIC was selected (Log-logistic).
  - For all other analyses (ITC for FOLFIRI, analyses vs trifluridine-tipiracil, analyses vs BSC) PFS is used as the proxy for time on treatment, in the absence of time to treatment discontinuation data for the comparators. This ensures that the same method could be used for both model arms.
- Utilities:
  - Based on mean pre- and post-progression EQ-5D data from BEACON.
    - ◊ Encorafenib/cetuximab model arm uses data from the encorafenib/cetuximab trial arm.
    - ◊ FOLFIRI model arm uses data from the FOLFIRI/cetuximab subgroup of the control trial arm.

    - ◊ Trifluridine-tipiracil and BSC model arms use the mean of the encorafenib/cetuximab trial arm and FOLFIRI/cetuximab subgroup of the control trial arm.
- No intravenous wastage.
- Subsequent treatments limited to trifluridine-tipiracil/BSC in primary analyses (as per clinical practice).
  - BEACON trial-based subsequent treatments modelled in scenario analyses.
- All analyses are provided based on list prices.
- All analyses provide deterministic point estimates of costs, QALYs and ICERs.
- For results presentation:
  - For primary analyses, results for the full range of parametric models are presented.
  - For scenarios, the best fitting model is used based on assessment of mean AIC/BIC across relevant trial arms.
    - ◊ For comparisons with FOLFIRI, this is based on mean AIC/BIC across the encorafenib/cetuximab and control arms in BEACON.
    - ◊ For comparisons with trifluridine/tipiracil, this is based on mean AIC/BIC across the encorafenib/cetuximab arm from BEACON and the trifluridine-tipiracil arm from RECOURSE.
    - ◊ For comparisons with BSC, this is based on mean AIC/BIC across the encorafenib/cetuximab arm from BEACON and the BSC arm from Kim 2018.

2.2 Encorafenib/cetuximab versus FOLFIRI

In response to ACD Section 3.34:

- *Modelling of encorafenib plus cetuximab and of FOLFIRI:*
  - *Cost-effectiveness results using the May 2020 data cut from BEACON CRC (see ACD section 3.18).*
  - *Cost-effectiveness results using the hazard ratio from the indirect treatment comparison applied to survival outcomes to adjust for the presence of cetuximab (see ACD section 3.21).*
  - *Cost-effectiveness results using the clinical efficacy data from BEACON CRC (see ACD section 3.20).*
  - *A full range of piecewise extrapolations for estimating overall survival of encorafenib plus cetuximab and of FOLFIRI (see ACD sections 3.19, 3.20 and 3.21).*
  - *Analyses adjusting overall survival and costs for subsequent trial treatments not used in NHS clinical practice, with methods and assumptions fully reported (see ACD sections 3.10 and 3.24).*
  - *Cost-effectiveness results using Kaplan–Meier data from BEACON CRC to model progression-free survival (see ACD section 3.22).*
  - *Cost-effectiveness results applying 10% drug wastage for oral treatments (see ACD section 3.29).*
  - *Cost-effectiveness results using time to treatment discontinuation (see ACD section 3.27).*

The following have been provided:

- Description of primary analyses and scenarios alongside pairwise ICERs in Table 2 (***Note:*** *primary analyses are shown in shaded rows and best fitting models by AIC/BIC are presented in bold text*).
- Detailed pairwise deterministic results and narratives in Section 2.2.1 onwards.

Table 2: Key parameters for revised pairwise analyses versus FOLFIRI

	Key parameters	Additional comments	ICER	Cross-reference
PF F1: ITC	• FOLFIRI survival curves: ITC • PFS for time on treatment	NA	Gompertz: £71,922 Log-normal: £81,099 **Log-logistic: £82,791** Gen. gamma: £96,502 Weibull: £115,477 Exponential: £133,963	2.2.1
PF F1a: cost of subsequent tx	As PF F1 plus • Costs of main subsequent txs from BEACON trial included	• OS piecewise using best fitting model (log-logistic)	£80,011	2.2.2.1
PF F1b: oral drug wastage	As PF F1 plus • 10% oral wastage	• OS piecewise using best fitting model (log-logistic)	£83,390	2.2.2.2
PF F2: BEACON control	• FOLFIRI survival curves: BEACON control arm • TTD for time on treatment	NA	Gompertz: £123,830 Log-normal: £145,417 **Log-logistic: £158,682** Gen. gamma: £176,510 Weibull: £201,318 Exponential: £232,419	2.2.1
PF F2a: cost of subsequent tx	As PF F2 plus • Costs of main subsequent txs from BEACON trial included	• OS piecewise using best fitting model (log-logistic)	£153,757	2.2.2.1
PF F2b: oral drug wastage	As PF F2 plus • 10% oral wastage	• OS piecewise using best fitting model (log-logistic)	£159,848	2.2.2.2

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; NA, not applicable; OS, overall survival; PF, Pierre Fabre; PFS, progression-free survival; TTD, time to treatment discontinuation; txs, treatments.

2.2.1 Primary economic analyses versus FOLFIRI

2.2.1.1 Model fits

As per ERG analyses, and in line with the Committee's preference, our new analyses use OS data fitted piecewise, such that Kaplan-Meier is used to 2.8 months, followed by parametric model fitting from that point. Two specific approaches are taken, depending on the analyses undertaken:

- For analyses that utilise BEACON data from the encorafenib **and** control arms, the same approach is applied to both arms.

- For analyses that utilise the FOLFIRI ITC, the piecewise approach is applied to the encorafenib arm only, to which the FOLFIRI HR from the ITC is applied to generate FOLFIRI survival curves.

Six parametric models were considered, and AIC/BIC statistics are presented in Table 3. Based on the lowest mean AIC/BIC across the two BEACON trial arms, the best fitting model to the OS curves was log-logistic. This is once again consistent with the model used for both the August 2019 data cut (company submission) and May 2020 data cut (technical engagement company response), when fitted from time zero. Although expert opinion could not be sought to validate the model fits on this piecewise approach for the fully validated May 2020 data cut, the long-term projections of the log-logistic model remain plausible, when comparing to these previous alternate estimates (Table 4). Similarly, the survival estimates projected by the piecewise log-logistic approach are similar to real world evidence for patients with BRAF-mutant mCRC treated with first-line chemotherapy (Nunes 2020 (4), as provided in the technical engagement company response). Clearly these patients are not directly comparable to BEACON given the different lines of therapy that patients are receiving. However, an interpretation of the results would be that when treating with encorafenib/cetuximab the prognosis is improved such that it is generally similar to that observed with a patient who is being treated at first-line. This is not unexpected given the statistically significant OS benefits observed with the encorafenib regimen versus standard chemotherapies in the BEACON trial.

The log-logistic once again fits the observed data best in terms of AIC/BIC statistics and may give the most plausible predictions of long-term survival based on previous clinical expert opinion.

In contrast the exponential model, as used by the ERG on the August 2019 data cut, is one of the worst fitting based on AIC/BIC statistics, and remains a highly pessimistic prediction of survival when applied piecewise to the May 2020 data cut, which lacks clinical face validity based on the low projected survival estimates it generates (Figure 1 and Table 5).

Table 3: AIC/BIC for parametric models fit to BEACON OS data; May 2020 data cut, models fit from 2.8 months onwards

Model	AIC			BIC		
	Encorafenib/ cetuximab	Control	Mean	Encorafenib/ cetuximab	Control	Mean
Exponential	1020.28	874.31	947.30	1023.59	877.44	950.51
Generalised gamma	1014.23	869.37	941.80	1024.15	878.74	951.45
Gompertz	1012.05	870.01	941.03	1018.67	876.26	947.46
Log-logistic	1012.12	868.76	940.44	1018.74	875.01	946.87
Log-normal	1014.91	868.32	941.62	1021.53	874.57	948.05
Weibull	1015.98	874.33	945.16	1022.6	880.58	951.59

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

Table 4: Encorafenib/cetuximab OS estimates based on trial Kaplan-Meier, piecewise parametric model fits and real-world evidence (%)

	1-yr	1.5 yrs	2-yr	2.5 yr	3-yr	4-yr	5-yr
BEACON August 2019 KM	41.5	26.9	NA	NA	NA	NA	NA
BEACON May 2020 KM	[redacted]	[redacted]	[redacted]	[redacted]†	NA	NA	NA
Company log-logistic (Aug 2019)	41.0	25.9	17.7	12.8	9.8	6.2	4.4
Company log-logistic (May 2020)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company piecewise log-logistic (May 2020)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company piecewise exponential (May 2020)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG piecewise exponential (Aug 2019)	41.7	24.7	14.7	8.7	5.2	NA	0.7
Nunes 2020 RWE‡ (4)	-	-	20	-	12	5	-

KM, Kaplan-Meier; NA, not available; OS, overall survival RWE, real-world evidence; yr, year. † 2.5 year estimate is subject to some uncertainty due to low numbers of patients at risk; ‡ estimates by visual inspection of survival curve from patients with BRAF-mutant mCRC treated with first-line chemotherapy.

Figure 1: Comparison of parametric models fitted to BEACON encorafenib/cetuximab OS Kaplan Meier curves (May 2020)

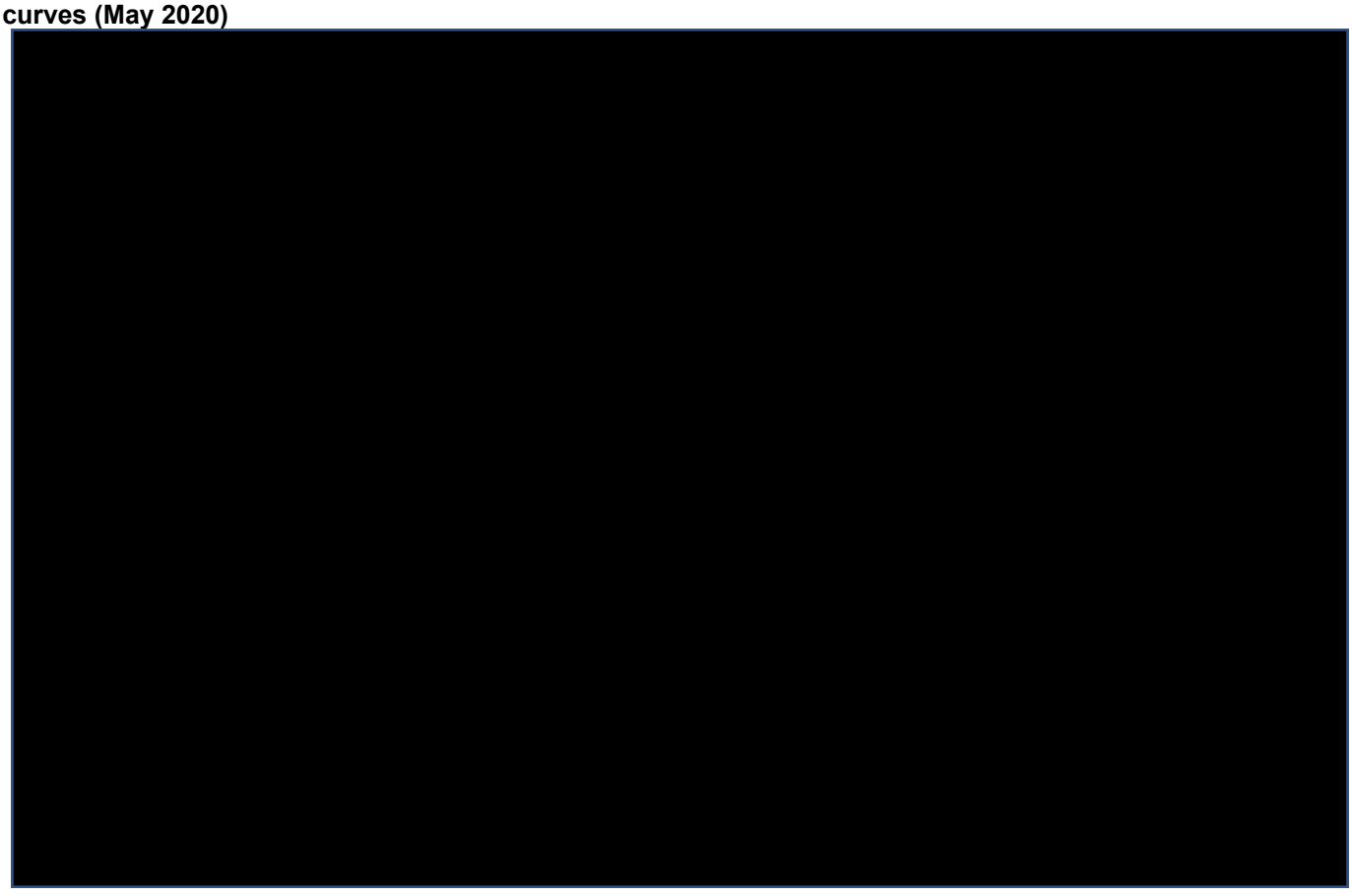


Table 5: Encorafenib/cetuximab OS estimates for piecewise parametric model fits (%)

Model	1-yr	3-yr	5-yr
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

OS, overall survival; yr, year.

2.2.1.2 ITC versus control arm for FOLFIRI effectiveness

As previously acknowledged in both the company submission and technical engagement response, we recognise there is uncertainty in the estimates of FOLFIRI effectiveness generated using the ITC. Nonetheless we maintain that using the control arm from BEACON would overestimate the survival estimates for FOLFIRI alone, given that the control arm included cetuximab, and thus underestimate the cost-effectiveness of the encorafenib regimen.

Using the piecewise BEACON encorafenib/cetuximab OS curve (log-logistic) from May 2020, to which the FOLFIRI ITC HR is applied, generates estimates of survival for FOLFIRI of [redacted]% at year 1, [redacted]% at year 2, [redacted]% at year 3, with a median survival of [redacted] months (Table 6). Median OS estimates for FOLFIRI identified in our company submission systematic literature review in BRAF-mutant mCRC, ranged between 4.2 and 5.7 months (5-7). These are below that of the control arm from BEACON for which cetuximab was used in combination with the investigator's choice of chemotherapy ([redacted] months May 2020 data cut).

Further examination of FOLFIRI studies which reported Kaplan-Meier survival curves (5, 6) in BRAF-mutant populations provide limited additional information due to the small sample sizes enrolled. One-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 very low in both studies (n≤6) (5, 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 Kaplan-Meier: [redacted]%). Piecewise parametric models fitted to the BEACON control arm OS are provided in Figure 2, with time point estimates from each model provided in Table 7.

In conclusion, using the BEACON control arm as a proxy for FOLFIRI effectiveness would provide an overly pessimistic estimate of FOLFIRI effectiveness and underestimate the cost-effectiveness of the encorafenib regimen. Whilst Pierre Fabre recognises the uncertainty that exists due to the paucity of direct comparative evidence, (which may be anticipated given clinical opinion has consistently highlighted the lack of clinical effectiveness for FOLFIRI within the BRAF V600E mutant population), the ITC arguably reflects a more realistic estimate of FOLFIRI effectiveness than the BEACON control arm.

Table 6: FOLFIRI OS estimates (based on encorafenib/cetuximab data and ITC HR†) for piecewise parametric model fits (%)

Model	1-yr	3-yr	5-yr
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; yr, year.
†HR for relative effectiveness of FOLFIRI vs encorafenib/cetuximab obtained from ITC.

Figure 2: Comparison of parametric models fitted to BEACON control arm OS Kaplan Meier curves (May 2020)

Table 7: FOLFIRI OS estimates (based on BEACON control arm) for piecewise parametric model fits (%)

Model	1-yr	3-yr	5-yr
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

OS, overall survival; yr, year.

2.2.1.3 Results

Economic results are provided in Table 8 for comparisons using the ITC as an indirect estimate of FOLFIRI effectiveness and the BEACON control arm (PF F1) as a conservative proxy for FOLFIRI effectiveness (PF F2).

Table 8: Pairwise results versus FOLFIRI (best fitting models by AIC/BIC are presented in bold text)

Analysis	E+C cost (£)	F cost (£)	E+C LYG	F LYG	E+C QALYs	F QALYs	Δ cost (£)	Δ LYG	Δ QALYs	ICER
PF F1 (ITC)										
PF F1 Gompertz	£67,973	£12,611	1.85	0.62	1.21	0.44	£55,362	1.23	0.77	£71,922
PF F1 Log-normal	£67,943	£12,585	1.69	0.61	1.12	0.43	£55,358	1.08	0.68	£81,099
PF F1 Log-logistic	**£67,896**	**£12,610**	**1.67**	**0.61**	**1.11**	**0.44**	**£55,287**	**1.05**	**0.67**	**£82,791**
PF F1 Generalised gamma	£67,713	£12,586	1.50	0.61	1.00	0.43	£55,127	0.89	0.57	£96,502
PF F1 Weibull	£67,512	£12,579	1.34	0.61	0.91	0.44	£54,932	0.74	0.48	£115,477
PF F1 Exponential	£67,432	£12,697	1.26	0.63	0.86	0.45	£54,734	0.63	0.41	£133,963
PF F2 (BEACON control)										
PF F2 Gompertz	£75,459	£13,633	1.85	1.02	1.21	0.72	£61,826	0.83	0.50	£123,830
PF F2 Log-normal	£75,429	£13,664	1.69	0.98	1.12	0.69	£61,765	0.71	0.42	£145,417
PF F2 Log-logistic	**£75,382**	**£13,713**	**1.67**	**1.02**	**1.11**	**0.72**	**£61,669**	**0.65**	**0.39**	**£158,682**
PF F2 Generalised gamma	£75,199	£13,573	1.50	0.93	1.00	0.66	£61,626	0.57	0.35	£176,510
PF F2 Weibull	£74,998	£13,421	1.34	0.85	0.91	0.61	£61,577	0.49	0.31	£201,318
PF F2 Exponential	£74,918	£13,417	1.26	0.84	0.86	0.60	£61,501	0.42	0.26	£232,419

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.

2.2.2 Scenario analyses versus FOLFIRI

Scenario results are provided in Table 9, and discussed in Section 2.2.2.1 to 2.2.2.2.

Table 9: Pairwise scenario results versus FOLFIRI (log-logistic OS)

Analysis	E+C cost (£)	F cost (£)	E+C LYG	F LYG	E+C QALYs	F QALYs	Δ cost (£)	Δ LYG	Δ QALYs	ICER
PF F1a (ITC/ sub tx)	£68,335	£14,905	1.67	0.61	1.11	0.44	£53,430	1.05	0.67	£80,011
PF F1b (ITC/ wastage)	£68,296	£12,610	1.67	0.61	1.11	0.44	£55,687	1.05	0.67	£83,390
PF F2a (Control/ sub tx)	£75,821	£16,066	1.67	1.02	1.11	0.72	£59,756	0.65	0.39	£153,757
PF F2b (Control/ wastage)	£75,835	£13,713	1.67	1.02	1.11	0.72	£62,123	0.65	0.39	£159,848

Abbreviations: Δ, incremental; E+C, encorafenib with cetuximab; F, FOLFIRI; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; LYG, life years gained; PF, Pierre Fabre; QALY, quality-adjusted life year; tx, treatment.

2.2.2.1 Subsequent treatment

In response to ACD Section 3.34:

- *Analyses adjusting overall survival and costs for subsequent trial treatments not used in NHS clinical practice, with methods and assumptions fully reported (see ACD sections 3.10 and 3.24).*

2.2.2.1.1 BEACON data

The BEACON study had a range of subsequent treatments after disease progression and as noted by the Committee some of these treatments included immunotherapies, which are not available at this point in the current treatment pathway in the NHS and which may prolong life. The Committee commented that if the subsequent treatments differed by trial arm and prolonged life, then the results of the intention-to-treat analyses would not be generalisable to the NHS.

A full list of subsequent treatments in the BEACON trial across the encorafenib/cetuximab and control arms is provided in Table 10 by drug class, with those used in ≥5% of patients in either arm highlighted in grey. (A more detailed table by individual drug is provided in Appendix 4 and was used to inform the cost scenario described in Section 2.2.2.1.2). A similar proportion of patients in both arms received subsequent treatments overall and the majority of these were standard chemotherapy agents (e.g. irinotecan, oxaliplatin, fluorouracil, folinic acid) or EGFR inhibitors (e.g. cetuximab).

Immunotherapy use (e.g. ipilimumab, pembrolizumab, nivolumab, durvalumab) was very low in both arms and lower in the encorafenib arm ([redacted] [redacted%] patients in the encorafenib arm and [redacted] [redacted%] patients in the control arm). It is therefore extremely unlikely that these agents would have had any influence on the survival estimates generated within the trial, and that the survival gains observed with the encorafenib regimen versus control would be driven by the intervention itself.

Bevacizumab was used in around [redacted]% of patients and usage was consistent across both arms. Any potential survival gains that could result from use of this therapy may be anticipated to impact on both arms to a similar magnitude.

We hope that the information provided in Table 10 is sufficient to address the concerns of the Committee as to the potential impact of subsequent immunotherapies on survival estimates. Analyses have not been possible (nor deemed relevant based on the information presented), to adjust survival estimates for subsequent treatments not available in the NHS.

Table 10: BEACON, subsequent systemic anti-cancer therapy by drug category

Category	Encorafenib/ cetuximab (N=220) n (%)	Control (N=221) n (%)
Any regimen	[redacted]	[redacted]
irinotecan combination + VEGFi	[redacted]	[redacted]
chemotherapy	[redacted]	[redacted]
irinotecan combination	[redacted]	[redacted]
kinase inhibitor	[redacted]	[redacted]
oxaliplatin combination	[redacted]	[redacted]
irinotecan + oxaliplatin combination + VEGFi	[redacted]	[redacted]
irinotecan	[redacted]	[redacted]
immunotherapy	[redacted]	[redacted]
irinotecan combination + EGFRi	[redacted]	[redacted]
EGFRi	[redacted]	[redacted]
irinotecan + VEGFi	[redacted]	[redacted]
oxaliplatin combination + VEGFi	[redacted]	[redacted]
other	[redacted]	[redacted]
irinotecan + EGFRi	[redacted]	[redacted]
chemotherapy + VEGFi	[redacted]	[redacted]
BRAFi + MEKi + EGFRi	[redacted]	[redacted]
BRAFi + EGFRi	[redacted]	[redacted]
BRAFi + EGFRi + irinotecan	[redacted]	[redacted]
immunotherapy + VEGFi	[redacted]	[redacted]
MEKi + immunotherapy	[redacted]	[redacted]
chemotherapy combination	[redacted]	[redacted]
irinotecan + EGFRi + immunotherapy	[redacted]	[redacted]
irinotecan + oxaliplatin + chemotherapy combination	[redacted]	[redacted]
kinase inhibitor + EGFRi	[redacted]	[redacted]
oxaliplatin combination + immunotherapy	[redacted]	[redacted]
chemotherapy + immunotherapy	[redacted]	[redacted]
irinotecan + oxaliplatin combination	[redacted]	[redacted]
irinotecan + oxaliplatin combination + BRAFi + MEKi + VEGFi	[redacted]	[redacted]
kinase inhibitor + immunotherapy	[redacted]	[redacted]
kinase inhibitor + other	[redacted]	[redacted]

Category	Encorafenib/ cetuximab (N=220) n (%)	Control (N=221) n (%)
oxaliplatin	[redacted]	[redacted]
BRAFi	[redacted]	[redacted]
BRAFi + MEKi + EGFRi + chemotherapy	[redacted]	[redacted]
BRAFi + MEKi + EGFRi + kinase inhibitor	[redacted]	[redacted]
BRAFi + MEKi + immunotherapy	[redacted]	[redacted]
BRAFi + MEKi+ immunotherapy	[redacted]	[redacted]
MEKi	[redacted]	[redacted]
MEKi + BRAFi + chemotherapy	[redacted]	[redacted]
VEGFi	[redacted]	[redacted]
chemotherapy + EGFRi	[redacted]	[redacted]
immunotherapy + other	[redacted]	[redacted]
irinotecan + oxaliplatin + VEGFi + immunotherapy	[redacted]	[redacted]
irinotecan + oxaliplatin combination + EGFRi	[redacted]	[redacted]

Terms are sorted in descending frequency of encorafenib/cetuximab column.

2.2.2.1.2 Economic analysis

The economic analyses provided in the company submission and the primary analyses presented herein (Table 8) assume that the cost of subsequent treatments includes only those that would be administered in NHS clinical practice (namely trifluridine-tipiracil and BSC). Scenario analyses are provided to account for the cost of treatments administered during the BEACON trial. To simplify the analysis, we considered only individual drugs that were received by ≥5% of patients in either trial arm. For treatments which were already included in the model (i.e. fluorouracil, folinic acid, irinotecan, cetuximab, trifluridine-tipiracil), dosing regimens were assumed to be the same as in their corresponding treatment regimens. For treatments which were not already included, SmPCs were used to determine dosing. NHS England National Dosing Tables were used where available. The CMU eMIT was used to determine costs of generic drugs. The BNF was used for all other treatments which were not listed in the eMIT. Where several formulations (i.e. concentrations or vial sizes) of a treatment were available, the average cost per treatment cycle was used, assuming that there would be equal usage of each formulation. Two model cycles of subsequent treatment were assumed, and costs were incurred in a lump sum at the point of disease progression. Administration costs were applied on a per-treatment basis. The proportion of patients who received each individual treatment is shown in Table 11, based on use of any individual drug in ≥5% of either of the encorafenib/cetuximab or control arms of BEACON. For trifluridine-tipiracil, where no subsequent therapy information was available, usage of subsequent therapy was assumed to be the mean of the E+C and control arms of BEACON. Full information is provided in the accompanying Excel model.

Results from this scenario analysis are provided in Table 9, showing a small reduction in the ICERs.

Table 11: Subsequent treatment usage rates used in scenario analyses

Subsequent therapy	Encorafenib/ cetuximab	Control (used for FOLFIRI)	Average (used for trifluridine-tipiracil)
Aflibercept	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]	[redacted]
Folinic acid	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]
Trametinib	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]

2.2.2.2 Oral wastage

In response to ACD Section 3.34:

- *Cost-effectiveness results applying 10% drug wastage for oral treatments (see ACD section 3.29).*

The primary analyses provided in Table 8 assume no wastage of oral therapies. This scenario assumed that 90% of patients would not waste any therapies, and that 10% of patients would waste some tablets in a pack by rounding up to the nearest whole pack. This was implemented in an identical way to how IV treatments are costed in the model. Results of this scenario are provided in Table 9 showing a very modest increase in the ICERs.

2.3 Encorafenib/cetuximab versus trifluridine-tipiracil

In response to ACD Section 3.34:

- *Cost-effectiveness results adjusting RECOURSE survival curves from the trifluridine–tipiracil arm to account for differences in prognosis in the population in RECOURSE and in BEACON CRC (see ACD section 3.16)*

The following have been provided:

- Description of primary analyses and scenarios alongside pairwise ICERs in Table 12 (***Note:*** *primary analyses are shown in shaded rows and best fitting models by AIC/BIC are presented in bold text*).
- Detailed pairwise deterministic results and narratives in Section 2.3.1 onwards.

Table 12: Key parameters for revised pairwise analyses versus trifluridine-tipiracil

	Key parameters	Additional comments	ICER	Cross-reference
PF T1: Peeters 2015 BRAF HR adjustment	• Tri-tip survival curves: RECOURSE survival curves, fully parametric models, with BRAF HR adjustment applied from Peeters 2015 – OS HR 4.0 – PFS HR 3.57 • PFS for time on treatment	NA	Gompertz: £55,111 Log-normal: £61,753 **Log-logistic: £63,109** Gen. gamma: £71,232 Weibull: £81,167 Exponential: £82,324	2.3.1
PF T1a: cost of subsequent tx	As PF T1 plus • Costs of main subsequent txs from BEACON trial included	• OS piecewise using best fitting model (log-logistic)	£60,244	2.3.2.1
PF T1b: oral drug wastage	As PF T1 plus • 10% oral wastage	• OS piecewise using best fitting model (log-logistic)	£63,585	2.3.2.2
PF T2: Safaee 2012 BRAF HR adjustment	• Tri-tip survival curves: RECOURSE survival curves, fully parametric models, with BRAF HR adjustment applied from Safaee 2012 – OS HR 2.24 – PFS HR as per OS • PFS for time on treatment	NA	Gompertz: £59,789 Log-normal: £67,827 **Log-logistic: £69,221** Gen. gamma: £79,303 Weibull: £92,147 Exponential: £96,588	2.3.1
PF T2a: cost of subsequent tx	As PF T2 plus • Costs of main subsequent txs from BEACON trial included	• OS piecewise using best fitting model (log-logistic)	£65,889	2.3.2.1
PF T2b: oral drug wastage	As PF T2 plus • 10% oral wastage	• OS piecewise using best fitting model (log-logistic)	£69,754	2.3.2.2

	Key parameters	Additional comments	ICER	Cross-reference
PF T3: Richman 2009 BRAF HR adjustment	• Tri-tip survival curves: RECOURSE survival curves, fully parametric models, with BRAF HR adjustment applied from Richman 2009 – OS HR 1.82 – PFS HR 1.14 • PFS for time on treatment	NA	Gompertz: £59,901 Log-normal: £69,629 **Log-logistic: £70,960** Gen. gamma: £81,395 Weibull: £95,722 Exponential: £103,081	2.3.1
PF T3a: cost of subsequent tx	As PF T3 plus • Costs of main subsequent txs from BEACON trial included	• OS piecewise using best fitting model (log-logistic)	£68,357	2.3.2.1
PF T3b: oral drug wastage	As PF T3 plus • 10% oral wastage	• OS piecewise using best fitting model (log-logistic)	£71,536	2.3.2.2

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; NA, not applicable; OS, overall survival; PF, Pierre Fabre; PFS, progression-free survival; TTD, time to treatment discontinuation; tx(s), treatment(s).

2.3.1 Primary economic analyses versus trifluridine-tipiracil

2.3.1.1 Model fits

AIC/BIC statistics for BEACON (encorafenib/cetuximab) and RECOURSE (trifluridine-tipiracil) OS data are provided in Table 13. Log-logistic is the best fitting model based on the lowest mean AIC and BIC.

Table 13: AIC/BIC for parametric models fit to BEACON (May 2020 data cut) and RECOURSE OS data

Model	AIC			BIC		
	Encorafenib/ cetuximab	RECOURSE	Mean	Encorafenib/ cetuximab	RECOURSE	Mean
Exponential	1020.28	2438.367	1729.3235	1023.59	2442.647	1733.1185
Generalised gamma	1014.23	2360.107	1687.1685	1024.15	2372.948	1698.549
Gompertz	1012.05	2408.46	1710.255	1018.67	2417.02	1717.845
Log-logistic	1012.12	2353.473	1682.7965	1018.74	2362.034	1690.387
Log-normal	1014.91	2371.367	1693.1385	1021.53	2379.928	1700.729
Weibull	1015.98	2369.837	1692.9085	1022.6	2378.398	1700.499

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

2.3.1.2 Choice of BRAF-mutant adjustment

As per the ACD Section 3.16/3.23, the Committee concluded that the RECOURSE OS curves should be adjusted to account for differences in BRAF mutation status since BRAF V600E leads to reduced OS, but that the cost-effectiveness results for encorafenib plus cetuximab compared with trifluridine–tipiracil would be very uncertain. The Committee recalled that it would consider

cost-effectiveness analyses that used a range of hazard ratios (HRs) to adjust for differences in the populations between BEACON and RECOURSE.

We provide three sets of economic analyses using different sources of BRAF-mutant adjustment, as described below. Higher HRs are indicative of a larger negative impact of BRAF-mutation on patient prognosis.

- **Safaee 2012 (8)** conducted a systematic literature review and meta-analysis of 26 cohort and RCT studies. The mean HR reported for OS indicates a substantial detrimental impact of BRAF-mutation (2.24 for BRAF mutant versus BRAF wild-type) and was statistically significant ($p<0.0001$). Individual OS HRs from the included studies range between 1.2 and 4.5. HRs for the impact on PFS were not reported in this meta-analysis.
- **Peeters 2015 (7)**, which post-dates the Safaee meta-analysis provide HRs at the higher end of the range (OS, 4.0; PFS, 3.57). This study was selected in our original submission as the only one to provide separate HRs for OS and PFS and which were identified via the clinical systematic literature review conducted in support of the submission.
- **Richman 2009 (9)** was selected by the ERG as being a UK-based study and was reported by Safaee et al. HRs reported in this study were 1.82 for OS and 1.14 for PFS.
- While the Peeters study could be viewed as an optimistic scenario, the Richman study is likely to be an overly pessimistic estimate of how trifluridine-tipiracil may perform specifically in a BRAF-mutant population.
- Overall, the HR provided by Safaee 2012 can arguably be considered as the most robust estimate of the poor prognosis associated with BRAF mutation given that it was derived from multiple studies identified by way of systematic review.

Note: An additional UK-based study was mentioned in the committee meeting as being reported by Safaee et al. Although this is correct (Maughan 2011 (10)), this study only reported HRs for the impact of any mutation (BRAF or RAS), rather than HRs for the impact of BRAF-mutation specifically. In the absence of a HR for the impact of BRAF-mutation specifically, this study could not be used to inform new economic analyses.

2.3.1.3 Trifluridine-tipiracil versus FOLFIRI

When considering how effective trifluridine-tipiracil may be in the BRAF-mutant mCRC population, the Committee can be directed to the choices that clinicians make from current therapies and the sequence of these treatments, to aid their discussions. It is clear from clinical experts and from NICE's own technology appraisal guidance that trifluridine-tipiracil is predominantly used in patients who have had 2 or more prior lines of therapy (See ACD Section 3.4), and that FOLFIRI would be given earlier in the pathway. Indeed, as noted in the company technical engagement response (See Section 2.1 Response, Figure 1) trifluridine-tipiracil appears to perform worse earlier in the treatment pathway, based on subgroup data from RECOURSE trial (2 prior regimens versus 4+ prior regimens).

This treatment sequencing would reflect improved effectiveness and tolerability of FOLFIRI versus trifluridine-tipiracil and this view has been consistently supported by clinical opinion; as stated by one clinical expert consulted by NICE (Harpreet S Wasan; Committee Papers) "…trifluridine-tipiracil is not particularly effective in the majority of mCRC".

As such, when considering by how much the survival curves from RECOURSE may need to be adjusted for the poorer prognosis observed with BRAF mutation, it would be expected that the resulting survival curves would lie some way to the left of those for FOLFIRI, equating to poorer survival with trifluridine-tipiracil compared with FOLFIRI.

2.3.1.4 Results

Economic results are provided in Table 14 for comparisons using BRAF-mutant adjustment hazard ratios from Peeters (PF T1), Safaee (PF T2) and Richman (PF T3).

Table 14: Pairwise results versus trifluridine-tipiracil (best fitting models by AIC/BIC are presented in bold text)

Analysis	E+C cost (£)	T cost (£)	E+C LYG	T LYG	E+C QALYs	T QALYs	Δ cost (£)	Δ LYG	Δ QALYs	ICER
PF T1 (Peeters 2015)										
PF T1 Gompertz	£67,973	£14,120	1.85	0.34	1.21	0.24	£53,853	1.51	0.98	£55,111
PF T1 Log-normal	£67,943	£14,876	1.69	0.37	1.12	0.26	£53,067	1.32	0.86	£61,753
PF T1 Log-logistic	**£67,896**	**£14,782**	**1.67**	**0.38**	**1.11**	**0.26**	**£53,114**	**1.29**	**0.84**	**£63,109**
PF T1 Generalised gamma	£67,713	£14,873	1.50	0.37	1.00	0.26	£52,840	1.12	0.74	£71,232
PF T1 Weibull	£67,512	£14,674	1.34	0.37	0.91	0.26	£52,837	0.97	0.65	£81,167
PF T1 Exponential	£67,432	£13,926	1.26	0.30	0.86	0.21	£53,506	0.96	0.65	£82,324
PF T2 (Safaee 2012)										
PF T2 Gompertz	£67,973	£15,610	1.85	0.49	1.21	0.34	£52,363	1.36	0.88	£59,789
PF T2 Log-normal	£67,943	£16,119	1.69	0.51	1.12	0.35	£51,824	1.18	0.76	£67,827
PF T2 Log-logistic	**£67,896**	**£15,943**	**1.67**	**0.51**	**1.11**	**0.35**	**£51,953**	**1.16**	**0.75**	**£69,221**
PF T2 Generalised gamma	£67,713	£16,066	1.50	0.51	1.00	0.35	£51,647	0.99	0.65	£79,303
PF T2 Weibull	£67,512	£16,110	1.34	0.51	0.91	0.35	£51,401	0.84	0.56	£92,147
PF T2 Exponential	£67,432	£15,430	1.26	0.46	0.86	0.32	£52,002	0.80	0.54	£96,588
PF T3 (Richman 2009)										
PF T3 Gompertz	£67,973	£18,748	1.85	0.56	1.21	0.39	£49,224	1.29	0.82	£59,901
PF T3 Log-normal	£67,943	£18,739	1.69	0.58	1.12	0.41	£49,204	1.10	0.71	£69,629
PF T3 Log-logistic	**£67,896**	**£18,532**	**1.67**	**0.58**	**1.11**	**0.41**	**£49,364**	**1.08**	**0.70**	**£70,960**
PF T3 Generalised gamma	£67,713	£18,899	1.50	0.57	1.00	0.40	£48,814	0.93	0.60	£81,395
PF T3 Weibull	£67,512	£18,878	1.34	0.57	0.91	0.40	£48,634	0.77	0.51	£95,722
PF T3 Exponential	£67,432	£18,766	1.26	0.55	0.86	0.39	£48,665	0.71	0.47	£103,081

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; T, trifluridine-tipiracil.

2.3.2 Scenario analyses versus trifluridine-tipiracil

Scenario results are provided in Table 15, and discussed in Section 2.3.2.1 to 2.3.2.2.

Table 15: Pairwise scenario results versus trifluridine-tipiracil

Analysis	E+C cost (£)	T cost (£)	E+C LYG	T LYG	E+C QALYs	T QALYs	Δ cost (£)	Δ LYG	Δ QALYs	ICER
PF T1a (Peeters/ sub tx)	£68,335	£17,633	1.67	0.38	1.11	0.26	£50,703	1.29	0.84	£60,244
PF T1b (Peeters/ wastage)	£68,296	£14,782	1.67	0.38	1.11	0.26	£53,514	1.29	0.84	£63,585
PF T2a (Safaee/ sub tx)	£68,335	£18,883	1.67	0.51	1.11	0.35	£49,453	1.16	0.75	£65,889
PF T2b (Safaee/ wastage)	£68,296	£15,943	1.67	0.51	1.11	0.35	£52,353	1.16	0.75	£69,754
PF T3a (Richman/ sub tx)	£68,335	£20,782	1.67	0.58	1.11	0.41	£47,553	1.08	0.70	£68,357
PF T3b (Richman/ wastage)	£68,296	£18,532	1.67	0.58	1.11	0.41	£49,764	1.08	0.70	£71,536

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; T, trifluridine-tipiracil.

2.3.2.1 Subsequent treatment

In response to ACD Section 3.34:

- *Analyses adjusting overall survival and costs for subsequent trial treatments not used in NHS clinical practice, with methods and assumptions fully reported (see ACD sections 3.10 and 3.24).*

Results from this scenario analysis are provided in Table 15, in line with the methodology described in Section 2.2.2.1 for comparisons of encorafenib/cetuximab with FOLFIRI. ICERs showed a small reduction in this scenario.

2.3.2.2 Oral wastage

In response to ACD Section 3.34:

- *Cost-effectiveness results applying 10% drug wastage for oral treatments (see ACD section 3.29).*

Results from this scenario analysis are provided in Table 15, in line with the methodology described in Section 2.2.2.2 for comparisons of encorafenib/cetuximab with FOLFIRI. ICERS showed a very modest increase in this scenario.

2.4 Encorafenib/cetuximab versus BSC

2.4.1 Relevance of BSC as a comparator

For clarity, Pierre Fabre anticipate that the encorafenib/cetuximab regimen would be used predominantly ahead of FOLFIRI as a second-line therapy or, ahead of trifluridine-tipiracil as a third-line therapy, and on this basis we feel that BSC is not an appropriate comparator.

V600E BRAF-mutant mCRC is a highly 'aggressive' cancer, which rapidly progresses through standard cytotoxic chemotherapy, including FOLFOX and FOLFIRI. As reported in the company submission and in Section 2.2.1.2 of this response, median OS from second-line therapy with cytotoxic chemotherapy ranges between 4.2 and 5.7 months (5-7). During this time, a patient's condition deteriorates, as does their suitability and/or fitness for systemic treatment; patient preservation is a crucial consideration here for the treating clinician. Many oncologists also feel that trifluridine-tipiracil is not effective in V600E BRAF-mutant mCRC, and in these cases treating with this therapy may lose the patient valuable time, reducing patient preservation and quality of life.

Consequently, owing to rapid disease progression and the relative ineffectiveness of existing therapeutic options, in a pathway that treats patients with FOLFOXIRI followed by trifluridine-tipiracil it is highly unlikely that there would ***any*** prevalent patient population who would remain either fit enough, or indeed alive, who would be suitable to receive encorafenib/cetuximab. For this reason, we do not feel a comparison of encorafenib/cetuximab versus BSC is a relevant one for decision-making but have provided analysis upon request from the appraisal committee.

2.4.2 Economic analyses versus BSC

In response to ACD Section 3.34:

- *Additional supporting analyses: A comparison of encorafenib plus cetuximab with best supportive care at third line for people who have trifluridine–tipiracil at second line.*

Although Pierre Fabre believe that BSC is not a suitable comparator for the reasons described in Section 2.4.1, at the request of the Appraisal Committee, we have provided exploratory analyses comparing encorafenib/cetuximab with BSC.

2.4.2.1 Choice of survival data

Three studies were identified by the systematic literature conducted in support of the company submission that reported evidence from BRAF-mutant mCRC populations (Karapetis 2014 (11); Kim 2018 (12); Peters 2013 (13)). BRAF-mutant OS and PFS results are summarised in Table 16. None of these studies formed a connected network with the BEACON study to allow indirect comparison. As with the approach taken for trifluridine-tipiracil the studies were then assessed for their suitability for a naïve comparison, which required OS and PFS Kaplan-Meier survival curves to be reported.

- **Karapetis 2014** reported an OS curve for a subgroup of patients with BRAF-mutant mCRC but a PFS curve was absent. OS data informing the BRAF-mutant OS curve was limited to only 6 patients treated with BSC. The lack of a PFS curve and the very small sample size precluded this study from any meaningful analysis.

- **Kim 2018** included 128 patients with mCRC treated with BSC, of whom 11 had BRAF-mutant disease. Although the study publication did not report OS and PFS curves for the BRAF-mutant population, it did report curves for the overall population (Publication Figure 2A/2B). A hazard ratio was also reported for the relative impact of wild type disease versus BRAF-mutant disease on OS (Publication Figure 2E, HR, 0.33; 95% CI 0.17, 0.66). A hazard ratio for the relative impact of wild type versus BRAF-mutation was not reported for PFS.
- **Peeters 2013** included a subgroup of 6 patients with BRAF-mutant mCRC treated with BSC, but was excluded from further analysis because survival curves were not reported.

As such, we concluded that the Kim 2018 study was the most appropriate to enable an economic analysis with the encorafenib/cetuximab regimen. Kaplan-Meier survival curves (OS and PFS) for the BSC arm (Publication Figure 2A and 2B) were digitised, and alongside the number of patients at risk, an estimate of the individual patient data was constructed using the methods described in Guyot 2012 (14). This approach is consistent with the methods employed and described in the company submission for survival curves derived from the RECOURSE study for trifluridine-tipiracil. The survival curves were then adjusted for the poorer prognosis associated with BRAF-mutation, based on the OS hazard ratio reported in this study and consistent with the methods used for trifluridine-tipiracil. It should be noted that the adjustment hazard ratio is taken as the reciprocal of the reported result, to determine the detrimental impact of BRAF-mutation versus wild type disease (i.e. HR 3.03; 95% CI 1.52, 5.88). In addition, as the adjustment HR was only reported for OS, this is applied to both OS and PFS curves.

Table 16: Studies reporting in BRAF-mutant mCRC population with a BSC arm

Study/ reference	Line of therapy	Intervention	N	Median OS (months); HR (95% CI)	Median PFS (months); HR (95% CI)
CO.17 Karapetis 2014 (11)	≥2	BSC + cetuximab	4	1.77; HR: 0.84 (0.2, 3.58); p=0.81	Median NR; HR: 0.76 (0.19, 3.08); p=0.69
		BSC	6	2.97	NR
200100007 Kim 2018 (12)	≥2	BSC + panitumumab	9	4.1; HR: 0.39 (0.1, 1.51); p=0.1597	1.5; HR: 0.28 (0.07, 1.08); p=0.0502
		BSC	11	3.0	1.3
408 Peeters 2013 (13)	3	BSC + panitumumab	9	NR	Median NR; HR: 0.34 (0.09, 1.24); p=0.1035
		BSC	6	NR	Median NR

BSC, best supportive care; HR, hazard ratio; mCRC, metastatic colorectal cancer; NR, not reported; OS, overall survival; PFS, progression-free survival.

2.4.2.2 Model fits

When mean AIC and BIC were considered across the encorafenib/cetuximab arm of BEACON and the BSC arm of the Kim 2018 trial, there was little difference in AIC/BIC statistics across many of the models, with differences being well within the commonly-used rule of thumb that a difference of 3 in the AIC would be reason enough to choose a specific model (Table 17). Given that log-logistic was the best fitting model for comparisons with FOLFIRI and trifluridine-tipiracil, we would propose that, for consistency, log-logistic would be the most appropriate model fit for the BSC comparison.

Table 17: AIC/BIC for parametric models fit to BEACON (May 2020 data cut) and Kim 2018 OS data

Model	AIC			BIC		
	Encorafenib/ cetuximab	BSC	Mean	Encorafenib/ cetuximab	BSC	Mean
Exponential	1020.28	691.3282	855.8041	1023.59	694.1803	858.88515
Generalised gamma	1014.23	684.3128	849.2714	1024.15	692.8689	858.50945
Gompertz	1012.05	690.6273	851.33865	1018.67	696.3314	857.5007
Log-logistic	1012.12	687.2268	849.6734	1018.74	692.9309	855.83545
Log-normal	1014.91	684.2519	849.58095	1021.53	689.9559	855.74295
Weibull	1015.98	686.5105	851.24525	1022.6	692.2145	857.40725

AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; OS, overall survival.

2.4.2.3 Summary of key parameters and results

The following have been provided:

- Description of key parameters alongside pairwise ICERs in Table 18.
- Detailed pairwise deterministic results in Table 19.

Table 18: Key parameters for revised pairwise analyses versus BSC

	Key parameters	Additional comments
PF BSC1	• BSC survival curves: Kim 2018 digitised survival curves (Kim 2018, Figure 2A, 2B), fully parametric models, with BRAF HR adjustment applied from same study – OS HR 3.03 (Kim 2018, Figure 2E, inverse of published value 0.33) – PFS HR 3.03 (assumed equal to OS) • PFS for time on treatment	• Adverse event rates and associated costs assumed to be zero • Costs of BSC assumed to be those associated with normal health state resource use for pre- and post-progression and are consistent with the approach used to cost BSC as a subsequent treatment in the original company submission • Subsequent treatment limited to BSC only

Abbreviations: BSC, best supportive care; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table 19: Pairwise scenario results versus BSC (best fitting model by AIC/BIC are presented in bold text)

Analysis	E+C cost (£)	BSC cost (£)	E+C LYG	BSC LYG	E+C QALYs	BSC QALYs	Δ cost (£)	Δ LYG	Δ QALYs	ICER
PF BSC1 Gompertz	£67,065	£8,959	1.85	0.38	1.21	0.28	£58,106	1.47	0.94	£62,113
PF BSC1 Log-normal	£67,053	£8,965	1.69	0.39	1.12	0.28	£58,088	1.30	0.83	£69,673
PF BSC1 Log-logistic	**£66,996**	**£8,985**	**1.67**	**0.40**	**1.11**	**0.29**	**£58,012**	**1.27**	**0.82**	**£71,164**
PF BSC1 Generalised gamma	£66,813	£8,992	1.50	0.40	1.00	0.29	£57,821	1.10	0.71	£80,993
PF BSC1 Weibull	£66,584	£9,017	1.34	0.40	0.91	0.30	£57,567	0.94	0.62	£93,490
PF BSC1 Exponential	£66,430	£8,879	1.26	0.35	0.86	0.26	£57,551	0.91	0.60	£95,597

Abbreviations: Δ, incremental; BSC, best supportive care; E+C, encorafenib with cetuximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PF, Pierre Fabre; QALY, quality-adjusted life year.

3 BEACON data May 2020 data cut

Kaplan-Meier data for the BEACON trial for the May 2020 data cut are provided in the following sections. BEACON OS data has been fully validated since the first committee meeting resulting in minor changes to the numbers of patients at risk. May 2020 data for PFS, PPS and TTD have also been provided in response to a request from the Appraisal Committee.

May 2020 Kaplan-Meier data is provided as follows:

- OS and PFS by **event or censor** for encorafenib/cetuximab and control for the overall population.
- OS, PFS, PPS and TTD by **event or reason for censoring** for encorafenib/cetuximab and control for the overall population.

3.1 OS (by event or censor, Enco/cetux and control)

Table 20: BEACON OS Kaplan-Meier data (May 2020 data cut)

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]			

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

OS, overall survival.

3.2 PFS (by event or censor, Enco/cetux or control)

Table 21: BEACON PFS Kaplan-Meier data (May 2020 data cut)

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient ID	Treatment arm	Event/ censoring time (months)	CENSOR
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

PFS, progression-free survival.

3.3 OS (by event or reason for censor, Enco/cetux and control)

Table 22: BEACON OS Kaplan-Meier data, Enco/cetux (May 2020 data cut)

		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
[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]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[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 *	Lost to Follow-up *
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
[redacted]					

OS, overall survival. * Reason for Censoring.

Table 23: BEACON OS Kaplan-Meier data, Control (May 2020 data cut)

		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
[redacted]					

		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
[redacted]					

		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
[redacted]					

		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
[redacted]					

		Events			
Timepoint	N at risk	Death	Ongoing Without Event *	Withdrawal of Consent *	Lost to Follow-up *
[redacted]					

OS, overall survival. * Reason for Censoring.

3.4 PFS (by event or reason for censor, Enco/cetux and control)

Table 24: BEACON PFS Kaplan-Meier data, Enco/cetux (May 2020 data cut)

		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 Tumor Assessments *
[redacted]										

		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 Tumor Assessments ***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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	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 Tumor Assessments *
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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	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 Tumor Assessments *
[redacted]										

		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 Tumor Assessments *
[redacted]										

PFS, progression-free survival. * Reason for Censoring.

Table 25: BEACON PFS Kaplan-Meier data, Control (May 2020 data cut)

		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 Tumor Assessments *
[redacted]										

		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 Tumor Assessments ***
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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	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 Tumor Assessments *
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[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	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 Tumor Assessments *
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										

PFS, progression-free survival. * Reason for Censoring.

3.5 PPS (by event or reason for censor, Enco/cetux and control)

Table 26: BEACON PPS Kaplan-Meier data, Enco/cetux (May 2020 data cut)

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]								

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]								

d, day; LTFU, lost to follow-up; PPS, post-progression survival.

Table 27: BEACON PPS Kaplan-Meier data, Control (May 2020 data cut)

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]								

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]								

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Obs	AVAL_d_final	death	on_going	consent_withdrawal	LTFU	study_end	number_left	number_at_risk
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

d, day; LTFU, lost to follow-up; PPS, post-progression survival.

3.6 TTD (by event or reason for censor, Enco/cetux and control)

Table 28: BEACON TTD Kaplan-Meier data, Enco/cetux (May 2020 data cut)

		Events/Censors		Events (details)								
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Unacceptable Aes Or Failure To Tolerate Study Drug	Withdrawal Of Consent
[redacted]												

		Events/Censors		Events (details)								
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Unacceptable Aes Or Failure To Tolerate Study Drug	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]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[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/Censors		Events (details)								
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Unacceptable Aes Or Failure To Tolerate Study Drug	Withdrawal Of Consent
[redacted]												

		Events/Censors		Events (details)								
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Unacceptable Aes Or Failure To Tolerate Study Drug	Withdrawal Of Consent
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Events/Censors		Events (details)								
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Unacceptable Aes Or Failure To Tolerate Study Drug	Withdrawal Of Consent
[redacted]												

TTD, time to treatment discontinuation. * Reason for Censoring
[a] Dose Interruption = Dose Interruption Of > 28 Consecutive Days (Encorafenib Or Binimetinib) Or 2 Missed Consecutive Irinotecan, 5-Fu, Or Fa Or >4 Missed Consecutive Cetuximab Doses

Table 29: BEACON TTD Kaplan-Meier data, Control (May 2020 data cut)

		Events/Censors		Events (details)									
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Receipt Of Subsequent Anti-Cancer Therapy	Unacceptable Aes Or Failure To Tolerate Study Drug	Withdrawal Of Consent
[redacted]													

		Events/Censors		Events (details)									
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Receipt Of Subsequent Anti-Cancer Therapy	Unacceptable Aes Or Failure To Tolerate Study Drug	Withdrawal Of Consent
[redacted]													

		Events/Censors		Events (details)									
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Receipt Of Subsequent Anti-Cancer Therapy	Unacceptable Aes Or Failure To Tolerate Study Drug	Withdrawal Of Consent
[redacted]													

		Events/Censors		Events (details)									
Timepoint	N at risk	Treatment Complete	Treatment Ongoing*	Changes In The Patient's Condition Or Development Of An Intercurrent Illness	Death	Dose Interruption [a]	Other	Patient Decision To Discontinue Study Treatment	Physician Decision	Progressive Disease	Receipt Of Subsequent Anti-Cancer Therapy	Unacceptable Aes Or Failure To Tolerate Study Drug	Withdrawal Of Consent
[redacted]													

TTD, time to treatment discontinuation. * Reason for Censoring

[a] Dose Interruption = Dose Interruption Of > 28 Consecutive Days (Encorafenib Or Binimetinib) Or 2 Missed Consecutive Irinotecan, 5-Fu, Or Fa Or >4 Missed Consecutive Cetuximab Doses.

4 Appendix: BEACON subsequent treatments by individual drug

Table 30: BEACON, subsequent systemic anti-cancer therapy by ATC class and preferred term

ATC level 4[a] preferred term[a]	Encorafenib/ cetuximab (N=220) n (%)	Control (N=221) n (%)
Any subsequent therapy	[redacted]	[redacted]
Pyrimidine analogues	[redacted]	[redacted]
Fluorouracil	[redacted]	[redacted]
Tas 102	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Gimeracil w/oteracil potassium/tegafur	[redacted]	[redacted]
Hua kang da	[redacted]	[redacted]
Calcium folinate w/fluorouracil	[redacted]	[redacted]
Floxuridine	[redacted]	[redacted]
Tipiracil;trifluridine	[redacted]	[redacted]
Other antineoplastic agents	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Aflibercept	[redacted]	[redacted]
Irinotecan hydrochloride	[redacted]	[redacted]
Bnc105	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Eribulin mesilate	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]
Tas 116	[redacted]	[redacted]
Tas 120	[redacted]	[redacted]
Detoxifying agents for antineoplastic treatment	[redacted]	[redacted]
Folinic acid	[redacted]	[redacted]
Calcium folinate	[redacted]	[redacted]
Calcium levofolinate	[redacted]	[redacted]
Levofolinic acid	[redacted]	[redacted]
Sodium folinate	[redacted]	[redacted]
Monoclonal antibodies	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Cetuximab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Panitumumab	[redacted]	[redacted]
Monoclonal antibodies	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Durvalumab	[redacted]	[redacted]
Gsk 3359609	[redacted]	[redacted]
Ramucirumab	[redacted]	[redacted]
Tremelimumab	[redacted]	[redacted]

ATC level 4[a] preferred term[a]	Encorafenib/ cetuximab (N=220) n (%)	Control (N=221) n (%)
Tsr 042	[redacted]	[redacted]
Protein kinase inhibitors	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]
Binimetinib	[redacted]	[redacted]
Encorafenib	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]
Trametinib	[redacted]	[redacted]
Cobimetinib	[redacted]	[redacted]
Platinum compounds	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Antivirals	[redacted]	[redacted]
Trifluridine	[redacted]	[redacted]
Folic acid and derivatives	[redacted]	[redacted]
Levofolinic acid	[redacted]	[redacted]
Folic acid	[redacted]	[redacted]
Other therapeutic products	[redacted]	[redacted]
Tipiracil	[redacted]	[redacted]
Cobicistat	[redacted]	[redacted]
Tipiracil hydrochloride	[redacted]	[redacted]
Not coded	[redacted]	[redacted]
Antineoplastic agents	[redacted]	[redacted]
Investigational antineoplastic drugs	[redacted]	[redacted]
General nutrients	[redacted]	[redacted]
Immunostimulants	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]
Investigational drug	[redacted]	[redacted]
Nitrogen mustard analogues	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Other alkylating agents	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Other cytotoxic antibiotics	[redacted]	[redacted]
Mitomycin	[redacted]	[redacted]
Selective immunosuppressants	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Vinca alkaloids and analogues	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
Bisphosphonates	[redacted]	[redacted]
Zoledronic acid	[redacted]	[redacted]
Combinations of antineoplastic agents	[redacted]	[redacted]
Dabrafenib w/trametinib	[redacted]	[redacted]
Other drugs affecting bone structure and mineralization	[redacted]	[redacted]
Denosumab	[redacted]	[redacted]

ATC level 4[a] preferred term[a]	Encorafenib/ cetuximab (N=220) n (%)	Control (N=221) n (%)
Other immunostimulants	[redacted]	[redacted]
Activated t-lymphocytes	[redacted]	[redacted]
Yttrium (90y) compounds	[redacted]	[redacted]
Yttrium (90 y)	[redacted]	[redacted]

5 References

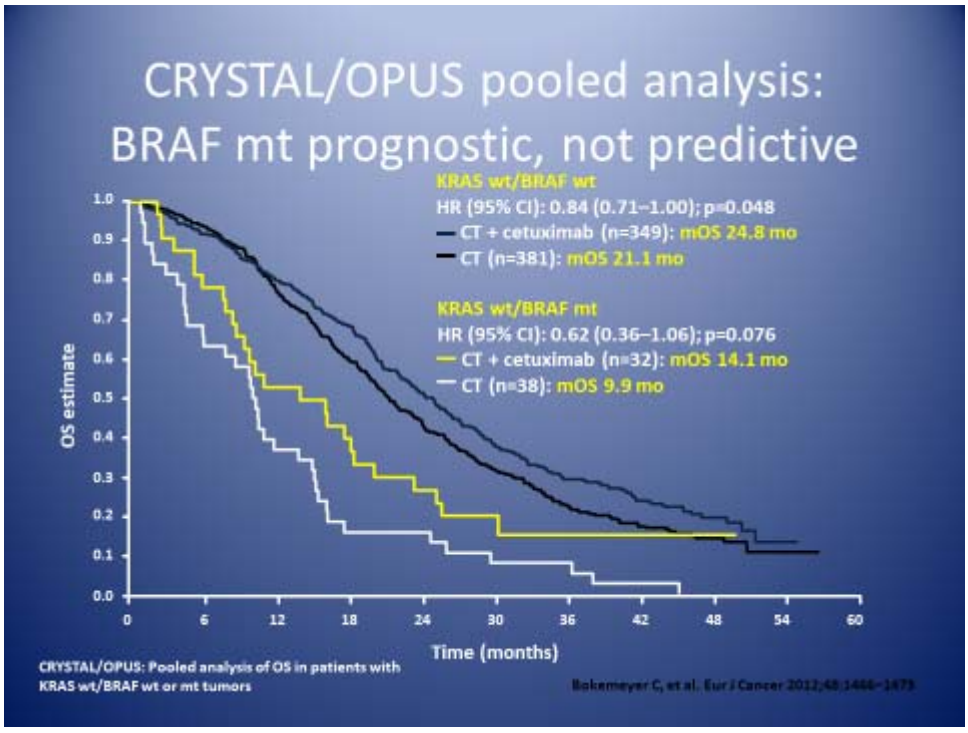
1. Clarke SJ, Yip S, Brown C, van Hazel GA, Ransom DT, Goldstein D, et al. Single-agent irinotecan or FOLFIRI as second-line chemotherapy for advanced colorectal cancer; results of a randomised phase II study (DaVINCI) and meta-analysis [corrected]. Eur J Cancer. 2011;47(12):1826-36.
2. Graeven U, Arnold D, Reinacher-Schick A, Heuer T, Nusch A, Porschen R, et al. A randomised phase II study of irinotecan in combination with 5-FU/FA compared with irinotecan alone as second-line treatment of patients with metastatic colorectal carcinoma. Onkologie. 2007;30(4):169-74.
3. Pierre Fabre. Data-On-File BEACON CRC 5th May 2020 datacut, OS data, Control arm treatment subgroups.
4. 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.
5. Yoshino T, Portnoy DC, Obermannova R, Bodoky G, Prausova J, Garcia-Carbonero R, et al. Biomarker analysis beyond angiogenesis: RAS/RAF mutation status, tumour sidedness, and second-line ramucirumab efficacy in patients with metastatic colorectal carcinoma from RAISE-a global phase III study. Ann Oncol. 2019;30(1):124-31.
6. Wirapati P, Pomella V, Vandenbosch B, Kerr P, Maiello E, Mark G, et al. Velour trial biomarkers update: Impact of RAS, BRAF, and sidedness on aflibercept activity. Journal of Clinical Oncology Conference. 2017;35(15 Supplement 1).
7. 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.
8. 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.
9. Richman SD, Seymour MT, Chambers P, Elliott F, Daly CL, Meade AM, et al. 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. J Clin Oncol. 2009;27(35):5931-7.
10. Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, et al. 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 (London, England). 2011;377(9783):2103-14.
11. Karapetis CS, Jonker D, Daneshmand M, Hanson JE, O'Callaghan CJ, Marginean C, et al. PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer--results from NCIC CTG/AGITG CO.17. Clin Cancer Res. 2014;20(3):744-53.
12. Kim TW, Elme A, Park JO, Udrea AA, Kim SY, Ahn JB, et al. Final Analysis of Outcomes and RAS/BRAF Status in a Randomized Phase 3 Study of Panitumumab and Best Supportive Care in Chemorefractory Wild Type KRAS Metastatic Colorectal Cancer. Clin Colorectal Cancer. 2018;17(3):206-14.
13. Peeters M, Oliner KS, Parker A, Siena S, Van Cutsem E, Huang J, et al. Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase III study of metastatic colorectal cancer. Clin Cancer Res. 2013;19(7):1902-12.

14. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.

I am commenting on this document on behalf of the RCP as Chair of the adjuvant and advanced NCRI sub group but also in my role as GI team lead for the West of Scotland and a PI on the BEACON and ANCHOR studies. I am writing as I am really disappointed by the initial response and hope there is still time to reconsider.

As I understand from the ACD conclusions the biggest area of committee uncertainty relates to the effect of the comparative treatments. There are some fundamental issues with using the BEACON study control arm as a proxy for FOLFIRI, and attempting to then decide re how it fits within colorectal pathways in the UK given that FOLFIRI Cetuximab is not a standard of care in the UK, but was mandated at the time by the FDA. I therefore support the approaches made to try and adjust for the impact of cetuximab when added to FOLFIRI, recognizing various scenarios exist for modelling what the actual control arm should have been and what effect the cetuximab may or may not have had. From personal experience and using the data from CRYSTAL I would estimate that cetuximab would add approximately six weeks to survival compared to FOLFIRI or irinotecan alone. We can see below that both BRAF mutant and wild type patients do gain benefit from cetuximab it's just that the prognostic aspect of being BRAF mutant means patients still do much less well overall.

Furthermore, it should also be noted that whilst the BEACON control arm included clinician's choice of either FOLFIRI, or irinotecan (in addition to cetuximab) it is widely accepted that patients tolerate FOLFIRI significantly better than single agent irinotecan.



Most importantly, in a group of patients who could potentially have orphan status (<10% of colon patients) and for whom we have made no advances in several decades until this novel doublet, it would seem (given the paucity of comparative data) appropriate to conclude that cetuximab has played a part in the control arm and that therefore the gain for the patients in the experimental arm is actually likely to be more rather than less predicted. At this point I would also like to highlight the concept of "proportional survival" for patients who are approaching end of life. An additional 4 or 5 months when you were only given six to live in the first place is quite different to the same amount of additional time if your estimated survival is measured in years not a short amount of months.

I would also like to highlight that this is actually a very small number of patients and any impact on the NHS budget overall should be fairly negligible – from my estimates it would only be 20 patients per year in Scotland and 200-300 patients per year across the whole of the UK. Whilst appreciating budget impact may be less relevant to NICE decision making, the relative unmet need and rarity of the BRAFV600E mutation should be taken into account.

Finally, as the BEACON trial allowed second or third line patients to be enrolled if I understand correctly NICE are making the assumption that the novel doublet would be as useful to patients in the third line setting. Our own audit data of the WOSCAN population showed that very few patients are fit enough for second line treatment (well below 50%) and none made it to third line treatment. Lonsurf has been approved but most clinicians accept that it is predominantly useful in patients with 'slow burn' disease and is certainly not deemed to be equivalent to FOLFIRI. Nor would one ever consider BRAF mutant patients to have 'slow burn' disease (those who are not refractory at the outset, have non visceral metastases, and who have responded to prior oxaliplatin and irinotecan based treatments). I cannot think of any situation where a clinician would use lonsurf prior to irinotecan or oxaliplatin based lines of treatment. This is contrary to the encorafenib/ cetuximab doublet where in fact two thirds of the patients in the trial where second line – i.e. clinicians would recruit to the trial rather than use conventional second or third line treatments. The pivotal Lonsurf trial did not drill down to the response based on RAS or BRAF but my personal experience is that it is extremely unlikely that a BRAF mutant patient would respond to Lonsurf and I would never choose to use this first should the novel doublet be approved. Looking to the future it seems likely that immunotherapy will be more helpful for the subset of patients who are BRAF mutant and MSI unstable and I would estimate the numbers who would be treated with encorafenib and cetuximab would drop further.

I would urge NICE to reconsider its provisional response given the current lack of effective treatment options available. This is a small group of patients, often young, who have never had a bespoke treatment for their sub type of cancer. The treatment is very well tolerated and also has less AE's which means in the context of the ongoing COVID scenario it's an extremely helpful option to have for patients. It also involves less chair time which is critical in the current era of social distancing and capacity and negates the need for a PICC line. This small sub group of patients do so much worse than all other colon patients – and worse than most other solid tumour patients presenting with stage IV disease. It is only with giving our best treatments as soon as possible i.e. first or second line that we can open up options for further studies and incremental gains in survival. I find it very difficult to contemplate that an approximately 50% gain in survival (5.9 to 9.3 months) for such a small number of patients (max 200) would not be approved. Likewise if it was approved for use in third line or beyond this would effectively mean no patients would live long enough to benefit from this treatment as in my own clinical experience only the minority of patients make it to second line and non to third line.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments end of Friday 25 September 2020 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Merck Serono Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links
Name of commentator person completing form:	[redacted], [redacted]

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments end of Friday 25 September 2020 **email:** NICE DOCS

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	In Section 3.11, the appraisal committee acknowledge there is limited evidence for people with BRAF V600E mutation-positive metastatic colorectal cancer and that "Encorafenib plus cetuximab is the first colorectal cancer treatment that targets the BRAF V600E mutation". This confirms the clinicians opinion that there is "currently no effective treatments for this type of colorectal cancer and encorafenib plus cetuximab represents a step change in treatment" also highlighted by the patients experts that explained "their cancer responded quickly to triple therapy (encorafenib plus binimetinib and cetuximab) and this was life-changing, whereas they saw little to no response on previous treatment." NICE committees are frequently called upon to make judgements based on incomplete or confounding information as clinical trial design can't always reflect the local practice which is shaped not only by clinical outcomes but also the local reimbursement landscape. The difficulty in defining a robust comparator on this occasion is reflective of the limited options available for these patients rather than a lack of efficacy, which has been clearly demonstrated through the trial results, is in line with clinical opinion and has been accepted by the committee. The committee remit to consider proper use of financial resources is also supported through this appraisal as the patient population size is limited in scope, identifiable through testing and is around 10% of the existing 1L mCRC who are BRAF mutant (Source: IPSOS, EPIC) (circa 1290 patient). Clinical experts have also confirmed that the patient response is frequently quick and quantifiable, further limiting the possibility of extensive prescribing without benefit.
2	In Section 3.13, the committee noted that the assumption of clinical equivalence between irinotecan + cetuximab and FOLFIRI + cetuximab was uncertain, despite the company submitting two randomized controlled trials which showed the two treatments did not differ statistically in OS and PFS for the second-line treatment of mCRC. This is supported by other studies (not in the company submission) which show irinotecan and FOLFIRI without cetuximab for the second-line treatment of mCRC do not differ statistically for OS or PFS (Clarke et al 2011, Graeven et al 2007).[1,2] **1.** Clarke et al. Eur J Cancer. 2011 Aug;47(12):1826-36. doi: 10.1016/j.ejca.2011.04.024. **2.** Graeven et al. Onkologie. 2007 Apr;30(4):169-74. doi: 10.1159/000099636.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with

Please return to: **NICE DOCS**

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

Consultation on the appraisal consultation document – deadline for comments end of Friday 25 September 2020 **email:** NICE DOCS

the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
It is a travesty that this drug has not been approved largely it would seem due to the cost of the medication regarding its efficacy, the lady who is the subject of the case study has survived for 3.5 years which is far more than she should have been due to her particular cancer. I appreciate that the NHS is not a bottomless pit of money but if there was someone properly overseeing the NHS funding and preventing millions being spent (and in many cases wasted due to poor case management) in clinical negligence cases this could probably fund the drugs, especially when there are limited people who would require the medication. It's a shameful decision.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Cost effectiveness as a measure how a treatment helps a person suffering from cancer should not be used. If a caner therapy has an effect on the cancer and allows the patient to continue to live, then it is most certainly cost effective. The psychological support a person and their family gain from having a therapy to keep them alive is immeasurable. I speak as a widow of a cancer patient. Are the recommendations sound and a suitable basis for guidance to the NHS? No - the question of cost effectiveness is a crude, painful and punative aspect. Those making this decision are condeming some people to seeing the end of life sooner than they need to.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

This medication appears to be effective in extending the lives of people with this particular type of bowel cancer and in improving their quality of life. There are no other treatments available. If this treatment can prolong the lives of people who have received this diagnosis and enable them to enjoy a quality of life, it must be made available.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

I disagree with the decision not to recommend Encorafenib plus cetuximab for treating BRAF V600E mutation-positive metastatic colorectal cancer in adults who have had previous systemic treatment. The committee concluded that there is an unmet need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer. Therefore, how can you deny patients the use of these drugs to give them a chance of life when there is no alternative available

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I believe that, this trial focused on a range of patients with a significantly higher age range than with similar trails for other specific mutations. It is known that bowel cancer developes more in over 55's and largely males. It seems unusual that is trial drug is not used to test for significant change in younger patients. If it is used as life prolonging drug for older patients the likelyhood of seeing life extending effects will be lower than in 18-40 year olds. One of the trial patients has expressed how this drug has helped them, whilst eliminating the spread of cancer without the need for chemotheropy. The trials need to be extended to provide proof that this drug can offer a long term solution to life reducing chemo and has a massively positive output for patients wellbeing.

Has all of the relevant evidence been taken into account?

If the evidence from this trial form a decision on the effectiveness it will be a flawed result as older patients will see less benefit.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Yes, given the demographic. Ot would be unfair to cost the treatment whilst it is being used as a coping drug rather than a cure. If there are patients that have used this to be cured, which I have been told is correct, then it needs to be continued to trial these effects and look at the demographic of patients who see significant changes from it's use.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. In terms of results more patients need to be trialed to gain evidence of effectivness. If this is to be used it needs to be in patients with a chance of life rather than a costly end of life substitute.

I believe that, this trial focused on a range of patients with a significantly higher age range than with similar trails for other specific mutations. It is known that bowel cancer developes more in over 55's and largely males. It seems unusual that is trial drug is not used to test for significant change in younger patients. If it is used as life prolonging drug for older patients the likelyhood of seeing life extending effects will be lower than in 18-40 year olds. One of the trial patients has expressed how this drug has helped them, whilst eliminating the spread of cancer without the need for chemotheropy. The trials need to be extended to provide proof that this drug can offer a long term solution to life reducing chemo and has a massively positive output for patients wellbeing.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

This is a small group of patients with a rare mutation. It is accepted there other forms of treatment for bowel cancer, do not work for them.

Has all of the relevant evidence been taken into account?

As was pointed out the evidence to support use, was based on studies using treatments not available/used in the NHS. Currently there are no specific treatments available for this mutation, however it has been proven to work

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

i would challenge this point as has previously been stated currently no other treatment available for this mutation

Obviously an emotive subject for those patients with the BRAF 600E mutation.

The difficulty I have understanding the decisions are:
1. It has been accepted to be effective.
2. Due to the rarity of the mutation there are a limited number of patients who would require the treatment.
3. It is accepted that the studies of current treatments used as a comparison (Beacon CRC)) are not used in the NHS . 4. 4. 4.That in fact there are no other options in the NHS.

Surely then this is an option to not only extend the life of patients in this group, but also the quality of that life

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Age

Has all of the relevant evidence been taken into account?

No

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Patients who took part in the trials have stated that their quality of life improved enormously because the adverse effects are manageable compared with other treatments. Please do not deny other patients with this rare form of cancer the opportunity to improve their quality of life.

Patients who took part in the trials have stated that their quality of life improved enormously because the adverse effects are manageable compared with other treatments. Please do not deny other patients with this rare form of cancer the opportunity to improve their quality of life. The basis of your conclusions is also age discriminatory.

Name	[redacted]
Role	

Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No. The economical reasoning is flawed This treatment should be approved for use for all suitable patients. Bowel cancel is the 2nd biggest cancer killer in the UK. This treatment has shown fantastic results for those who have been given the chance to use it. It is approved in EU. Disregarding it's efficacy on economic grounds is disappointing and is taking away hopes of a longer life for many affected by this type of cancer. Please approve its widespread use in the UK.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Recommending Encorafenib in combination with Cetuximab for patients with metastatic colorectal cancer with a BRAF V600E mutation is really important because it massively improves patients' quality of life. This is particularly important for young patients. In the existing study, the average patient was aged 60+. A high percentage of people obtain significant benefits from this drug.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? The trials were based upon 60year old patients, and discriminate against younger people with a better prognosis.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

It would appear that young people are an increasing group within this patient group. They are not being given life-extending options. It feels ageist to deny them a chance of a better quality of life. My fiance is 38 and we have made friends with other people in their 30s that have been diagnosed with the same mutation. In the last month alone 2 of these people have died. Both had young children. Had they been able to access these drugs they may well still be alive today. Please do not let this happen to my partner and many other like him.

Has all of the relevant evidence been taken into account?

I don't think the most recent data sets have been taken in to account. I understand that NICE guidelines are there for a reason and there is a sound integrity to them. However, I feel that some of the data analysis and qualitative and quantitative methods miss capturing real life stories and evidence. I am in a group of 250 people that are battling to find treatments for BRAF. They are pretty much all on the BEACON doublet (globally) and are having major benefit. It would seem standard practise in America and Australia to switch between standard chemotherapy options to BEACON and back as a way of slowing or containing this disease. This really needs to be looked at. Not only are we well behind on offering the BEACON doublet as a standard line of treatment but it has not even been established about using it interchangeably to increase life expectancy. We really do need the UK to get moving and step up to this unmet need. Don't let us slip further behind in our fight against cancer.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I don' think so. Talking with other experts and spending time with people who are lucky enough to access this drug combination there seems to be a real mismatch. In reality this drug combination is doing wonders for the under 50s and especially late 30s/early 40s. I am in contact with these patients and I have seen for myself over this year how they have improved.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Absolutely not. To withhold the only treatment available specifically for BRAF V600E mutation is barbaric and negligent. There is no other life-extender available for this large group of patients. To withhold this drug is unforgivable. As I have highlighted on my previous comments the UK needs to really get a grip on how far behind we are with standard care options for cancer.

Please consider negotiating further with Pierre Fabre to reduce the price of the drug combination. Even if you can't do that please allow this approval as it will take away the only option for extended survival that is currently available. The only other option left for patients if this is not approved is to travel to other countries to access it there. It feels wrong to not look after our own citizens.
I want to extend my fiances life for as long as possible. Buying time for other innovative treatments to become available and for surgical procedures to advance. We have raised funds, currently over £80,000, to create an innovative research program using CRISPR sequencing. We have a real opportunity to make a difference so please assist us by making this drug available to keep my partner alive long enough to benefit from this.

Recommendations

Encorafenib plus cetuximab is the first colorectal cancer treatment that targets the BRAF V600E mutation

Yes this is the first and only treatment available for patients with BRAF V600E. It has been a huge global, quality study with significant, reliable data. As you have highlighted yourselves.... it is the only targeted treatment available so to withhold treatment is cruel and unnecessary.

Clinical trial evidence shows that encorafenib plus cetuximab increases how long people live compared with FOLFIRI plus cetuximab or irinotecan plus cetuximab.

Here it is in print. Clinical trial evidence shows this combination works. It is the only treatment that works beyond first and second line treatments. To take this option away will end patients lives sooner and is an unthinkable move. There has been so little development around BRAF V600E that I as the carer to my fiance have set up a research project with University of Birmingham to fund a three year project and CRISPR sequencing to help find a cure for this chemo-resistant cancer. To take away a life-extending option also takes away my fiances chance to benefit from the ever changing landscape of new breakthroughs and developments.

But the cost-effectiveness estimates are higher than what is normally considered a cost-effective use of NHS resources, so it cannot be recommended for routine use in the NHS

The UK is embarrassingly falling well behind in the way we treat Cancer. Europe and other western countries are taking leaps and bounds. This drug combination is recognised as a step change to treat this mutation. To withhold under 'normally considered cost-effective' is yet another set of evidence that you are not prepared to move forward with bringing the UK at least inline with other countries.
I understand cost effectiveness being relevant when there are other effective treatments available. In this case this is the ONLY life extending treatment so some flexibility must be applied to help provide a standard of care to this patient group.

Collecting further data is unlikely to address the clinical uncertainty

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:
The company's adjustment of health utilities for the progression-free health state is more likely to reflect clinical practice.

Also, with the current economic modelling, encorafenib plus cetuximab does not have potential to be cost effective compared with current treatment

This makes no sense at all as it has already been recognised by you that 'Clinical trial evidence shows that encorafenib plus cetuximab increases how long people live compared with FOLFIRI plus cetuximab or irinotecan plus cetuximab' so to compare it's cost-effectiveness to treatments that are not SPECIFIC to BRAF V600E is ludicrous .

Committee discussion

Innovation Comment on section: Encorafenib plus cetuximab is an innovative treatment for BRAF V600E mutation-positive metastatic colorectal cancerEncorafenib plus cetuximab is an innovative treatment for BRAF V600E mutation-positive metastatic colorectal cancer

Yes it is! It is the first major breakthrough for this patient group. It is the only ray of light for my partner. With him being allowed to go on this treatment it buys us time and life. It buys us time to further research and to build treatment options via our own research program with University of Birmingham.
It is a chance for the UK to make steps to go back to being innovative and not lag in the fight against cancer.

Encorafenib with cetuximab is not recommended in the NHS

The committee considered that the most plausible ICER was currently above what NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, but it had not seen estimates reflecting its preferred modelling. It therefore concluded that it could not recommend encorafenib plus cetuximab for previously treated V600E mutation-positive colorectal cancer.

Surely a big buying power like the NHS can negotiate harder with Pierre Fabre to make this drug combination available? 15% of CRC have this mutation (Kopez) and it is recognised that more and more young people are being effected. My fiance is 38 and we have a large, growing network of patients that are coming to us, via our research project, that are young in age. Our Professor says that there is growing concern that this mutation is appearing more and more and in younger and younger people. We need to act on this now and give hope and options to these people. They should not be disregarded and left to an early death based on monetary guidelines when there are no other relevant options.

Proposed-date-for-review-of-guidance

If this drug combination is not given the go ahead then to not review the status for three years is unthinkable. Most patients with this BRAF mutation would die in that timescale without being able to access the only targeted treatment available to them.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No but I think you need to reconsider the drugs to make them more broadly available and a lot earlier in treatment. My [redacted] old sister has been on these drugs for 3 weeks and her latest bloods showed that her cancer markers have decreased by 75%. This is the ONLY POSITIVE news we have had since she was diagnosed with stage 4 on [redacted]. These drugs have given us as a family, including her [redacted] young children ([redacted], [redacted]yrs) hope for very first time.

Has all of the relevant evidence been taken into account?

No. You are not thinking about outcomes, the considerations are largely based on cost effectiveness and that is not how we should value medicine and treatment

Are the recommendations sound and a suitable basis for guidance to the NHS?

The NHS needs to reconsider the use of the drugs and start offering them sooner after people's diagnosis. My sister's life May be saved on these drugs, and other families should have access to them too. Money should not be a barrier to saving lives.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

Not enough weight has been given to the positive outcomes there have been for patients with BRAF mutant metastatic colorectal cancer whose prognosis is otherwise poor. Some are young and so the cost needs balancing with the importance of gaining a little more precious time - and it is only 10% of bowel cancer patients it affects. But their lives matter. We cannot overlook this.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No - they go against the findings of the European Commission and are inhumane - as well as not throwing them their final lifeline, this will affect the psychological well-being of these bowel cancer suffers as they face their final months.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - if this drug combination can provide more time and less neuropathy for these patients, it should be used. Quality and quantity of life have not been given enough weight.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
You mention it does meet the criteria for end of life but is too expensive. My understanding is that it not only is shown to extend that period of life, but also that it reduces chances of death by 39%. That percentage is worth spending money on. Or is there something better out there you know about? I'm not aware that there is.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
These drugs should be approved given the overwhelming evidence proving their efficacy. The time, even extended by a few months, for those suffering to be able to spend time sorting affairs, living some form of quality of life and spending time with loved ones (especially those with children whose lives will be scarred by loss) cannot be measured in £.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Please allow these drugs to be used on those who have already suffered from so many rounds of chemotherapy. Do not take away the only hope that some people have. Please!!!!

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Has all of the relevant evidence been taken into account?

My reading of the evidence is that is that committee did not feel that they had enough evidence to be certain of the degree of efficacy, although they were clear it met the criteria for a life extending treatment. Given this and given the lack of other treatments for this BRAF V600E mutation and the "life changing" improvements described by the experts by experience, my view is that the committee should make this drug available for prescription by expert oncologists.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

As above, the evidence on the exact amount of improvement is uncertain and the committee have decided to use this uncertain evidence not to support this potentially life changing treatment. My view is that the decision of the usefullneed of this particular drug for a particular patient should be left to clinicians. Use of this treatment could also lead to further understanding of this condition and additional treatments.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, I feel that this drug should be made available as a prescribing option for clinicians. The numbers who have the BRAF V600E are small and the number who will be suitable for this treatment are even smaller. This makes the cost not prohibitive and this is the only available treatment for this mutation. Use of this treatment leads to substantial improvement in quality of life and survival for patients. This will not only impact on patients but also on their families and loved ones. Use of this "game changing" treatment may also lead to development of other treatments for this aggressive cancer.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

While I understand that the cost-effectiveness of drugs must be of paramount concern to NICE and therefore the NHS, I would urge that you consider
A) the cost of chemotherapy, hospital admittance, other therapies for patients as well. In the case of v-600e, chemotherapy DOES NOT work for 90% of cases. Why the beacon treatment would therefore be considered a 2nd/3rd/4th/5th and in some cases 6th line treatment is beyond me. The data shows some positive outcomes for over 60% of patients (vs 10% on chemotherapy).

If we are to continue with current complications arising from Covid, a number of other therapies (including talking therapies, complimentary ones etc) have been suspended which has a massive effect on the overall health of patients. While it is expensive (£1400 for 42 capsules), surely the cost of keeping the patient alive, not in chemotherapy and perhaps not being constantly admitted to hospital, taking up chemo spaces of those whose chemotherapy is shown to work must be of some benefit.

I lost my sister in [redacted], who was due to begin this treatment then.
She was only accepted after 3 lots of failed chemotherapy. We knew in [redacted] it had a 10% chance of working for her.
What a waste of money for her staying in hospital with chemo complications, district nurse visits, pain relief from her growing tumours, and more importantly time. Time that a [redacted] year old woman (who was diagnosed as stage iv only 6 days after first feeling symptoms, but not told about her cancer being v600e until 2 MONTHS AFTER DIAGNOSIS) could have spent with her young daughter, her husband and family.

This cancer has robbed my family of a wonderful, brave and strong woman who, in our minds suffered needlessly because of the hoops she had to jump through in order to receive her treatment, which came too late for her.

Surely you need to look holistically at cost.
Look at WHO is typically diagnosed with this cancer.
My sister was an otherwise healthy, fairly young woman.
She was a tiny shell of a person by the end of her life. Her life and death could've been made more bearable by having this.

I know, as one of her consultants heartlessly told her, we were just 'buying some time'...but that's what we are all doing on this earth,

I would urge you to reconsider. To give people the chance to give this horrific mutation a good 'beating'.

For my sister, [redacted]

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Recommendations

If this drug combination has been shown to extend life, at end of life, for this very specific set of patients, and has actually already been in use within the NHS, why is it now being recommended to be stopped?
It seems cost-effectiveness is the main reason, which understandably has to be a major factor.
However, until a better option is developed, for those patients who were desperately hoping it would help provide a few months extra to spend with their families, it just seems cruel to take the chance away from them, leaving no other option but supportive care.
Clinical uncertainty is also mentioned, but if this combination is already being used, why is this?

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

I was diagnosed with bowel cancer at [redacted] years old. My daughter was [redacted] and son less [redacted] at the time.

My private healthcare covered my operation and chemo as they fell Under the NICE guidelines, but they have been very clear they will not cover any further treatment that is not approved by NICE. I make this point as it is startling to hear that should my cancer go metastatic I would not be eligible for this treatment either in the NHS or privately. I understand there are many variables to consider, I of course may not have this rate firm of vowel cancer, there may be other options. But for those eligible to receive such treatment there surely should be options made available for them that include newer, perhaps more costly treatments. If it had been shown to work it makes no sense not to approve it for relevant cancer sufferers in the U.K.

We need as a country need to move forward and invest in new treatments. If it's costs then perhaps come up with new ways of funding them so it's not an all or nothing.

I have had 4 years of time with my children thanks to surgery, if things had progressed I would have taken any risk and given anything for a few years more.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

I strongly feel that everyone should be giving access to these drugs since they have clearly proven to work in cases where other drugs have not.

I lost a very dear friend to cancer last year - metastatic cancer and who knows if she would still be with us here no if she would have had access to this drug!?

You cannot put a cost on life and to deny this as a possible drug on NHS.

It is simply has to be made as an offer to everyone there is no other option - everyone deserves there best changes to live!

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

THis is a very aggressive form of colorectal cancer which affects only a small proportion of mainly younger/middle aged women with metastatic bowel cancer. Therefore to deny this treatment to this group of women is discriminatory.
This drug treatment should be an option for all patients and give them choice. I support also that this should be an option for oncologists to prescribe to patients they feel could benefit.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

From the patients' perspective, I would hope the treatment could be prescribed even if it only prolonged life for a limited period of time . I am aware that the cost of the treatment is quite high, but it would only be given to a very small number of patients with this very aggressive form of CR cancer, and therefore not be a major drain on NHS resources .
I therefore think it would be unreasonable not to "give it a go".
Are the recommendations sound and a suitable basis for guidance to the NHS?

Research on this treatment has shown that that there is evidence that this helps patients by prolonging their life expectancy. At the moment there are few other treatments available which will have this effect.
I support the ability for this treatment to be an option for oncologists to have the opportunity to prescribe its use and for it to be fully funded and a real and funded choice for patients. Current treatments have been seen to be ineffective and therefore I would like to see a patient with this condition, who is most likely in medical terms to be a “young” person , given the opportunity to prolong their lives to spend quality time with their young families etc.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are the recommendations sound and a suitable basis for guidance to the NHS?

We understand that the treatment can be effective and is recognised as such in other countries. To parents of a daughter whose fiance, aged only 38, now needs to access such treatment to extend his life, it seems unfair to deny him this chance. They have both worked so desperately hard to keep him alive and to raise money (over £80,000 by over 1000 people) to support research, by Birmingham University, into treatments for the mutation. If sucessful this research will benefit 1000's of others.

Recommendations

Clinical trial evidence shows that encorafenib plus cetuximab increases how long people live compared with FOLFIRI plus cetuximab or irinotecan plus cetuximab.

You say that the above is not cost effective, yet you go on to state that it is the only treatment that extends life to those with BRAF V600E.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Is there any evidence that this strain affects a disproportionate group? If so this would impact negatively if this treatment option was not available

Has all of the relevant evidence been taken into account?

Comparing a like for like medication on different strains would not give an accurate picture or a fair comparison

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Cost effectiveness needs to be compared both short and long term - would this treatment option be a more cost effective option than having more frequent but less effective treatments for this strain. So having x amount of other treatment options for longer may be more expensive in the long term.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Having current treatment options based on a different strain is not a suitable basis - you cannot compare like for like in this scenario you have to look at the impact/benefit it would have for people with this particular type of cancer not just the generic heading of 'bowel cancer'

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

1. Standards of research evidence
The argument against funding of the Enco-cetuximab regimen suggests there is a lack of evidence that draws upon appropriate comparators. It is suggested that available evidence is based on comparisons made with control treatments that are inequivalent to NHS treatments. However, given the small pool of individuals within this patient group coupled with the significant lack of treatments available, it's is highly unlikely that a gold standard of evidence would be achieved. It has been suggested that the existing evidence from BEACON trials provide the most appropriate form of evidence available at present. By discounting this evidence, we feel many people will effectively be denied life extending opportunities due to unrealistic requirements of evidence. This is not in fitting with your acknowledgment that these individuals have an unmet treatment need requiring innovation to address.

2. Rarity of the patient group and cost effectiveness
We would ask NICE to consider the rarity of this patient group when evaluating cost effectiveness. This is a minority group within those treated for cancer (and indeed those being treated for colorectal cancer) and a group with so few

treatment options at present. As such, we feel thresholds for cost effectiveness should be lowered so as to redress the paucity of options for the individuals.

3. Inequitable opportunity
We understand that lines have to be drawn in access to treatments where changes in service provision occur. However, we feel that denying those who have commenced the application process provides an inequality in treatment. Again, this is likely to deny many people the opportunity to extend their life on the basis that they have not progressed past the application stage.

4. The voice of experts by experience
We would ask you to allow the accounts of the experts by experience to be given significant weight on your decision. Their experiences suggest not only a quick response to the triple therapy, but also highlight the significant impact of the many side effects inherent in existing treatments such as neuropathic damage. As well as extending lives, the Enco-cetuximab treatment has the potential to reduce these side effects which are so detrimental to ones quality of life in a period where time is so precious.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life.

Has all of the relevant evidence been taken into account?

No. A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No, Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy. A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy.

Please reconsider your refusal to recommend Encorafenib in combination with Cetuximab for patients with metastatic colorectal cancer with a BRAF V600E mutation because:
1 It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life.
2 Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy.
3 A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Please reconsider your refusal to recommend Encorafenib in combination with Cetuximab for patients with metastatic colorectal cancer with a BRAF V600E mutation because:
1 It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life.
2 Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy.
3 A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The current availability of this treatment is only after one or two alternative chemotherapy regimes have been completed. This may mean some do not survive to take advantage of this treatment reducing the costs and the percentage of potential recipients. On the other hand if it was available as a first line of defence

then the costs of the alternative routes must reduce the total cost of the encorafenib/cetuximab treatment over the period of treatment (3.3; 3.4; 3.6).

The psychological impact (3.2) of having the potential of an additional life expectancy and or reduction in side effects is immense although perhaps not quantifiable. However, again has the potential to reduce the burden for NHS support services in relation to counselling and medication.

Refusal to provide a known supportive therapy potentially denies an individual of their human right to life for as long as possible.

Has all of the relevant evidence been taken into account?

A more quantifiable impact assessment could be completed on the tangible effects of replacing 1st and 2nd stream first defence options with the Encorafenib/cetuximab treatment in relation to alternative costing models and mental support.

The current availability of this treatment is only after one or two alternative chemotherapy regimes have been completed. This may mean some patients do not survive to take advantage of this treatment reducing the costs and the percentage of potential recipients. On the other hand if it was available as a first line of defence then the costs of the alternative routes must reduce the total cost of the encorafenib/cetuximab treatment over the period of treatment (3.3; 3.4; 3.6).

The appraisal document notes that this treatment is less toxic and more manageable than the two most prevalent alternatives (3.2; 3.9; 3.31). This has the potential to reduce other medical costs in terms of Pharmaceutical medicines to deal with side effects eg neuropathic damage, antisickness medication, painkillers, together with potential tangible reductions for inpatient and out patient care.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

See previous answers Re harder to assess costs for supporting medication, healthcare and mental support for less successful treatments.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Encorafenib plus cetuximab meets NICE's criteria for being a life-extending treatment at the end of life. But the cost-effectiveness estimates are higher than what is normally considered a cost-effective use of NHS resources, so it cannot be recommended for routine use in the NHS.

From a Patient/recipients point of view cost is only one element. Quality of life, extension of life and impact on additional life supporting costs should also be considered.

As one emotive example I'm currently a patient receiving this treatment. I am expecting my first grandchild in the [redacted] and the thought that I may have lost this opportunity to see my first grandchild is devastating to both me and my family. This treatment provides such hope for maximising quality of life in what is know to be an overall short life time expectancy.

2.1 On 30 April 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product encorafenib (Braftovi)

Recommendations

Encorafenib plus cetuximab is the first colorectal cancer treatment that targets the BRAF V600E mutation, and could be used as second or third-line treatment.

Clinical trial evidence shows that encorafenib plus cetuximab increases how long people live compared with FOLFIRI plus cetuximab or irinotecan plus cetuximab.

These are both very important points.

Marketing authorisation indication

2.1 On 30 April 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for the medicinal product encorafenib (Braftovi)

committee-discussion

Encorafenib plus cetuximab is an innovative treatment for BRAF V600E mutation-positive metastatic colorectal cancer

This represents a ‘step change’ in treatment (3.1; 3.10; 3.31).

The appraisal document notes that this treatment is less toxic and more manageable than the two most prevalent alternatives (3.2; 3.9; 3.31). This has the potential to reduce other medical costs in terms of Pharmaceutical medicines to deal with side effects eg neuropathic damage, antisickness medication, painkillers, together with potential tangible reductions for inpatient and out patient care.

There is an unmet need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer

This is so important and offers a ‘step change’ (3.1;3.10; 3.31)

There is an unmet need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer
This treatment is only suitable for those with the BRAF V600E mutation which affects a small number of individuals (<10% of colorectal cancer patients) however can be ‘life changing’ (3.1)

The current availability of this treatment is only after one or two alternative chemotherapy regimes have been completed. This may mean some do not survive to take advantage of this treatment reducing the costs and the percentage of potential recipients. On the other hand if it was available as a first line of defence then the costs of the alternative routes must reduce the total cost of the encorafenib/cetuximab treatment over the period of treatment (3.3; 3.4; 3.6).

People would welcome an effective treatment option for BRAF V600E mutation-positive metastatic colorectal cancer

Absolutely.

As a current patient/recipient it has given me hope and positivity whilst recognising the long term limitations of life expectancy.

As one emotive example I'm currently a patient receiving this treatment. I am expecting my first grandchild [redacted] and the thought that I may have lost this opportunity to see my first grandchild is devastating to both me and my family. This treatment provides such hope for maximising quality of life in what is know to be an overall short life time expectancy.

The psychological impact (3.2) of having the potential of an additional life expectancy and or reduction in side effects is immense although perhaps not quantifiable. However, again has the potential to reduce the burden for NHS support services in relation to counselling and medication.

Encorafenib plus cetuximab may be used after 1 or more previous lines of treatment in clinical practice

The current availability of this treatment is only after one or two alternative chemotherapy regimes have been completed. This may mean some do not survive to take advantage of this treatment reducing the costs and the percentage of potential recipients. On the other hand if it was available as a first line of defence then the costs of the alternative routes must reduce the total cost of the encorafenib/cetuximab treatment over the period of treatment (3.3; 3.4; 3.6).

FOLFIRI and trifluridine–tipiracil are relevant comparators for encorafenib plus cetuximab after 1 previous line of treatment

It is the only drug recommended after first-line treatment for metastatic colorectal cancer in the NICE Pathway for colorectal cancer.

It is important to note that there are 'no further treatment options' which is a devastating realisation for patients.

The current availability of this treatment is only after one or two alternative chemotherapy regimes have been completed. This may mean some do not survive to take advantage of this treatment reducing the costs and the percentage of potential recipients. On the other hand if it was available as a first line of defence then the costs of the alternative routes must reduce the total cost of the encorafenib/cetuximab treatment over the period of treatment (3.3; 3.4; 3.6).

Trifluridine–tipiracil and best supportive care are relevant comparators for encorafenib plus cetuximab after 2 previous lines of treatment

The clinical experts agreed that encorafenib plus cetuximab could also be used when no other active treatment options are available. However, the clinical experts noted that at this stage people may not be well enough to have active treatment.

The current availability of this treatment is only after one or two alternative chemotherapy regimes have been completed. This may mean some do not survive to take advantage of this treatment reducing the costs and the percentage of potential recipients. On the other hand if it was available as a first line of defence then the costs of the alternative routes must reduce the total cost of the encorafenib/cetuximab treatment over the period of treatment (3.3; 3.4; 3.6).

Encorafenib plus cetuximab is clinically effective but the comparators in BEACON CRC are not used in the NHS

Results from the final August 2019 data cut showed that encorafenib plus cetuximab increased overall survival (9.3 months; 95% confidence interval 8.1 months to 11.3 months) more than the investigator's choice of FOLFIRI plus cetuximab or irinotecan plus cetuximab (5.9 months; 95% confidence interval

Using irinotecan in the control arm of BEACON CRC does not reflect clinical practice

Irinotecan was associated with worse toxicity and possibly worse outcomes than FOLFIRI and the committee had concluded that it was not a relevant comparator (see section 3.5)

The appraisal document notes that this treatment is less toxic and more manageable than the two most prevalent alternatives (3.2; 3.9; 3.31). This has the potential to reduce other medical costs in terms of Pharmaceutical medicines to deal with side effects eg neuropathic damage, antisickness medication, painkillers, together with potential tangible reductions for inpatient and out patient care.

Subsequent treatments in BEACON CRC do not reflect NHS clinical practice but may extend life

This represents a ‘step change’ in treatment (3.1; 3.10; 3.31).

Encorafenib plus cetuximab meets the criteria to be considered a life-extending end of life treatment

The clinical experts explained that the average life expectancy for people with BRAF V600E mutation-positive metastatic colorectal cancer was shorter than 2 years.

The appraisal document highlights on a number of occasions that this treatment has the potential to extend life (ref 1.1; Page 3; 3.2; 3.7; 3.30)

As one emotive example I’m currently a patient receiving this treatment. I am expecting my first grandchild [redacted] and the thought that I may have lost this opportunity to see my first grandchild is devastating to both me and my family. This treatment provides such hope for maximising quality of life in what is know to be an overall short life time expectancy.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

This drug could massively improve the quality of life for many battling bowel cancer and should be approved for use with immediate effect.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Has all of the relevant evidence been taken into account?

In arguing that that FOLFIRI is more appropriate to be considered the SOC in BRAF mt CRC than irinotecan, the committee is rather missing the point. Chemotherapy, regardless whether this is irinotecan or FOLFIRI is ineffective in BRAF mutant cancers. In particular, all these tumours are already 5FU refractory as they have had 1L treatment.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Have the team considered the relevant costs of admissions with chemotherapy related complications for example febrile neutropenia and diarrhoea, which do not happen on encorafenib plus cetuximab.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, it is inconceivable that this treatment should not be available to CRC patients with BRAF mutant cancers. In this life-limiting disease for which chemotherapy is very ineffective, there is now a treatment availble which improves overall survival by a substantial amount, with minimal toxicity.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the

grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Young age should be a consideration. I think this discriminates against young people for the following reasons -
1. My brother in law due to his young age was mis-diagnosed for approx 2 years before colon cancer which had spread to his liver was diagnosed. It has since spread to his lungs. It is unfair to penalise him when an earlier diagnosis could have prevented him from reaching the stage where he now needs this drug.
2. Younger people are less likely to be able to pay for this treatment privately and therefore should be entitled to this via the NHS.

Has all of the relevant evidence been taken into account?

The evidence outlined is not detailed and should not evidence be gathered directly to compare encorafenib plus cetuximab with FOLFIRI, and with trifluridine–tipiracil rather than indirectly?

Are the recommendations sound and a suitable basis for guidance to the NHS?

If this is the the first colorectal cancer treatment that targets the BRAF V600E mutation, shouldn't clinical trials in NHS clinical practice be encouraged?

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Age

NICE's decision to not fund the drugs due to clinical uncertainty over their benefits discriminates against younger patients. The study uses patients where the average age is 60-62 and this therefore denies younger people e.g. in their 30s a chance of life saving drugs. A few people in the study saw their tumours shrink away to nothing and younger patients with probably only one tumour following existing treatments might be those who have successful outcomes. These patients probably have young families and would also benefit enormously from a much greater quality of life by having oral medication instead of regimens of cytotoxic chemotherapy.

There are currently no licensed treatments available specifically for patients with tumours with BRAFV600E mutations and given the poor prognosis for these patients they deserve this opportunity (particularly the young). The trial shows the first ever significant advance for this group of patients using a treatment that is

easily administered and tolerated. This treatment has already been approved in both the USA and Europe and UK patients deserve an equal opportunity.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
An absolutely travesty that we spend billions supporting research to make the most of our incredible scientific developments that can save life's, including my husbands who has the BRAF V600 mutation to have it snatched it away by money! How can we put a cost of the life of a [redacted] old father of [redacted]!!! Devastated, please re-consider.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Recommendations How can you put a price on extending someone lift expectancy, especially those how are you with young families	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
The data is clear that this will provide sufferers and their family a lifeline and a chance to extend life significantly. This extra time could be the difference for parents to raise their children, children to know their parents and for patients to make precious memories.	

Name	[redacted]
Role	
Other role	

Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Please reconsider your refusal to recommend Encorafenib in combination with Cetuximab for patients with metastatic colorectal cancer with a BRAF V600E mutation because: 1 It is based upon age discrimination it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life. 2 Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy. 3 A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This proposal is discriminating against young patients on the basis of age –this is a study where the average age was 60-62 and you are using the results of that study to deny a young person (age [redacted]) his chance of life-saving drugs. Please reconsider your decision.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I'm alarmed that this option has been deemed too expensive an option by NICE for those suffering with aggressive forms of colon cancer. My [redacted] passed away aged [redacted], just 18 months after initial diagnosis and less that three months after confirmation of metastasis. He left behind [redacted] daughters, [redacted] grand daughters and was survived by his [redacted] year old mother. He was a hardworking professional who devoted his life to paying taxes yet trials were not an option to him. Perhaps this specific trial was not available during his illness. However, there are people living today who are in the exact same position that my father was; NICE has a duty of care to provide this life-extending treatment for those fighting against cancer today. Despite the wonders of our NHS, it sometimes feels as though we have cancer prevention and treatment of a third world country. NICE - please	

prioritise! This is important for so many people and those family members who will survive them.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes, age discrimination, there seems to be a large increase in younger people with bowel cancer that needs addressing and investigating. Your recommendations on Braf seem to be rather contradicting and confusing - "1.1 Encorafenib plus cetuximab is not recommended, within its marketing authorisation, for treating BRAF V600E mutation-positive metastatic colorectal cancer in adults who have had previous systemic treatment." And then I read this - "31 The patient and clinical experts explained that encorafenib plus cetuximab represents a step change in treatment for people with BRAF V600E mutation-positive colorectal cancer and there is high unmet need for an effective treatment. The committee was aware that there are no other BRAF V600E targeted treatments available for this population. The clinical experts explained that targeted treatment can change the genetic make-up of the tumour, potentially offering time and targets for other treatment options in the future. The committee noted that because the treatment is not a chemotherapy, it is transformative for people's quality of life. The committee concluded that encorafenib plus cetuximab is an innovative treatment for V600E mutation-positive colorectal cancer."

Has all of the relevant evidence been taken into account?

No, it doesn't look like it as you've arrived at the decision not to approve the drug yet you have sited it is the only relevant and targeted drug combination available. Why would you ignore your own evidence? " 31 The patient and clinical experts explained that encorafenib plus cetuximab represents a step change in treatment for people with BRAF V600E mutation-positive colorectal cancer and there is high unmet need for an effective treatment. The committee was aware that there are no other BRAF V600E targeted treatments available for this population. The clinical experts explained that targeted treatment can change the genetic make-up of the tumour, potentially offering time and targets for other treatment options in the future. The committee noted that because the treatment is not a chemotherapy, it is transformative for people's quality of life. The committee concluded that encorafenib plus cetuximab is an innovative treatment for V600E mutation-positive colorectal cancer." What is hazard ratios ? " Guessing "- not good enough, you even admit lack of data for people with Braf v600 -" The company and ERG highlighted the lack of data for people with BRAF V600E mutation-positive colorectal cancer". so looking at this more trials are needed, how can you move

forward with out trials to collect the data - “Uncertainties about comparative effectiveness were unlikely to be resolved by collecting further data because there were no ongoing studies using comparators relevant to UK clinical practice for encorafenib plus cetuximab. Also, the Cancer Drugs Fund would not collect data on comparator treatment.”

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

What cost effectiveness, how much money do you put on a life ? The NHS has just spent roughly 220 million on England’s nightingale hospitals at a rough cost of 15 million a month to run and saved how many lives ? Not many, and they wasted more on renting private hospitals - surly your committee can point this out to the NHS when applying for your preferred modelling budget - “Encorafenib plus cetuximab is effective and innovative but the cost-effectiveness estimates do not reflect the preferred modelling”

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. “The committee acknowledged that the company did not know the price of encorafenib plus cetuximab because cetuximab is supplied by another company and has a confidential discount. The committee recognised that encorafenib plus cetuximab was effective and innovative but had not seen cost-effectiveness estimates reflecting its preferred modelling.” how can you print this if you don’t know all your own data

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The BRAF mutation predominantly affects a small proportion of younger and middle aged women and to deny this treatment to this group of women is discriminatory. It should be an option for oncologists to prescribe to those patients that would benefit and where life would be extended.

Has all of the relevant evidence been taken into account?

There needs to be consideration on the success of trials in relation to the age and underlying health conditions of the participants. This is a disease that predominantly is apparent in young and middle aged women. These are small numbers of patients and therefore the costs need to take this into consideration.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

This is the only treatment for the BRAF mutation and the results have been very positive. This is a mutation that is predominantly prevalent in young and middle aged females, often who have no other underlying health issues. Clinical trials have been very positive and the extension to life needs to be taken into consideration along with the prognosis which is higher dependent on age and level of fitness. The cost effectiveness needs to be taken into account with the small numbers who would be eligible and the significant extension to life that could be achieved. The cost of treatment may be high but the small numbers who would be eligible would not result on it being a major drain on NHS resources. It should be made available in these circumstances, on the recommendation of oncologists who are experienced and managing the treatment of stage 4 patients.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I am a [redacted] year old [redacted] with metastatic bowel cancer and the BRAF mutation. I was diagnosed in [redacted] and I am currently responding well to folfoxiri as a first line treatment. I have no underlying health issues and this would be a 2nd or 3rd line treatment for me, hopefully to maintain and manage my cancer and enable me to live a much longer life than I would without it. This is the only treatment that is specifically for the BRAF mutation and clinical trials have been positive. The cost may be high but it would only be used after recommendation from experienced oncologists and it is not something that would be suitable for large numbers (causing an excessive drain to NHS resources). It is astounding to me that you can have a suitable treatment denied on the basis of cost for young and middle aged women who have families, careers and lives still to live. This should be a real and funded choice for patients. Current treatments have been seen to be ineffective and to deny this to a patient with this medical condition, likely to be a 'young' person, due to cost I do not believe to be a sound recommendation.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Refusal to provide a known supportive therapy potentially denies an individual of their human right to life for as long as possible.

Has all of the relevant evidence been taken into account?

NICE are not supporting it due to costs. The appraisal document notes that this treatment is less toxic and more manageable than the two most prevalent alternatives (3.2; 3.9; 3.31). This has the potential to reduce other medical costs in terms of Pharmaceutical medicines to deal with side effects eg neuropathic damage, antisickness medication, painkillers, together with potential tangible reductions for inpatient and out patient care. In addition, treatment times will not be longterm (circa two years ref 3.30). This is a treatment for months not years due to the aggressive nature of the BRAF mutation (3.16).

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

The psychological impact (3.2) of having the potential of an additional life expectancy and or reduction in side effects is immense although perhaps not quantifiable. However, again has the potential to reduce the burden for NHS support services in relation to counselling and medication.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The current availability of this treatment is only after one or two alternative chemotherapy regimes have been completed. This may mean some do not survive to take advantage of this treatment reducing the costs and the percentage of potential recipients. On the other hand if it was available as a first line of defence then the costs of the alternative routes must reduce the total cost of the encorafenib/cetuximab treatment over the period of treatment (3.3; 3.4; 3.6). This treatment is only suitable for those with the BRAF V600E mutation which affects a small number of individuals (<10% of colorectal cancer patients) however can be 'life changing' (3.1). The appraisal document highlights on a number of occasions that this treatment has the potential to extend life (ref 1.1; Page 3; 3.2; 3.7; 3.30) and this treatment meets an 'unmet need' for treatments for BRAF V600E (Page 5; 3.3; 3.31).

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life.

Has all of the relevant evidence been taken into account?

Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy.
A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy.
A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.

Are the recommendations sound and a suitable basis for guidance to the NHS?

1 It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life.
2 Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy.
3 A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.

Please reconsider your refusal to recommend Encorafenib in combination with Cetuximab for patients with metastatic colorectal cancer with a BRAF V600E mutation because:
1 It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life.
2 Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy.
3 A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Why are you denying the recommendation of treatment approved across Europe and the USA based solely on cost? The exact opposite of patient centered care and recommendations.	

Name	[redacted]
Role	
Other role	
Organisation	

Location	
Conflict	
Notes	
Comments on the ACD:	
This drug should be approved! How can you justify all the research and evidence that it works not to use such a good drug? Also how can you put a price on extending someone life? It disgusting that you treat people as just numbers and don't seem to care about improve their lives!	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are the recommendations sound and a suitable basis for guidance to the NHS? Please reconsider your refusal to recommend Encorafenib in combination with Cetuximab for patients with metastatic colorectal cancer with a BRAF V600E mutation because: 1 It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life. 2 Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy. 3 A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Recommendations Encorafenib plus cetuximab meets NICE's criteria for being a life-extending treatment at the end of life. But the cost-effectiveness estimates are higher than what is normally considered a cost-effective use of NHS resources, so it cannot be recommended for routine use in the NHS. I'm upset and concerned that this medical drug is not being approved for use under NHS 'resources' because of cost. The use of this drug is mostly complete, and only requires help to get it over the line and into mainstream use.	

Some patients are waiting for this potentially life saving drug treatment; patients who have had major life changing surgery and are still fighting.

The NHS absolutely should be providing this treatment; for many people this is a glimmer of hope to being able to overcome their battle.

Please give people a chance of a better life, because in all seriousness who can put a price on that.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes - unlawful discrimination by age. By using trial statistics with an average age of over 60 you are being discriminating towards young patients and denying these young patients their chance of life-saving drugs. It has been shown that for younger patients, the quality of life would be greatly improved with the use of Encorafenib plus cetuximab opposed to chemotherapy.

Has all of the relevant evidence been taken into account?

No. Research has shown that on average 75.9% of patients with metastatic colorectal cancer with a BRAF V600E mutation showed a complete response, partial response or a stable disease with this proposed treatment, compared with 31.2% for standard treatment. If this research and statistical evidence has been taken into account then this combination of drugs would have been recommended.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

The reason given for this negative recommendation is not due to cost.

Are the recommendations sound and a suitable basis for guidance to the NHS?

NO
The committee concluded that there is an unmet need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer. Therefore, how can you deny patients the use of these drugs to give them a chance of life when there is no alternative available.

Patients who took part in the trials have stated that their quality of life improved enormously because the adverse effects are manageable compared with other treatments. Please do not deny other patients with this rare form of cancer the opportunity to improve their quality of life.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

It is extremely disappointing that NICE have taken the decision not to support the use of this treatment on the NHS simply on the grounds of finance. How much is a person's life worth? There is no monetary value that can attributed to it. I am currently a cancer survivor but should things change I would hope that NICE are not making decisions on my treatment and survival based on monetary considerations. As far as I can see there are no clinical reasons why NICE should not approve the use of this treatment.
I sincerely urge you to reconsider your decision and give everyone who is suitable to be treated a chance of extending their life.
I appreciate finance is finite however the reports of the success of this treatment and the fact that it has been approved by many other countries including the EU should be swaying the decision process to allow the NHS to use this treatment.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

This recommendation is reverse age discrimination.
The study had an average age of 60+; by denying life-saving drugs to a younger group of adults based upon a study with an average age in their 60s, it is unlawfully denying a younger section of the population their chance of life; younger people may react better to the drug. My husband's nephew is 35 years with 4 year-old twins & he NEEDS this drug.

Has all of the relevant evidence been taken into account?

You deny the drug based on a study saying life expectancy only went up from 5.4 - 9 months, BUT another study showed some (eg [redacted]) went into complete remission.
It also does not take into account QUALITY of life - my husband's nephew (age [redacted]) now needs to spend the rest of his life on chemo without this drug, thus losing 1 week in 2 of the time he has left.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No - even if someone only gains 9 months rather than 5.4 months extra life, that is still a significant gain AND the quality of that life could be meaningful if chemo were avoided.

Some people (like [redacted]) have achieved complete remission.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - denies younger people their chance of life based on a study of (average age) 60+ years and takes no account of quality of life for those patients who are relying on chemo to keep them alive.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

these are a small but clinically disadvantaged group of patients
BRAF patients have a dismal prognosis and there is an unmet need at present though in the UK we can not use cetux 2nd line on the NS due to CDF restrictions, globally this is routinely used so I believe that using this as a second line comparator is acceptable and if anything beneficial to the control arm
also irinotecan can be used and is often interchanged for FOLFIRI

therefore I would NICE to consider that this is a meaningful combination for these patients who face a dismal outlook otherwise

Are the recommendations sound and a suitable basis for guidance to the NHS?

please see comments above

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

In regards to whether all of the evidence has been taken into account, there is a grey area with regards to the control arm - NICE have lent towards not approving rather than approving in the interpretation of the data and modelling they have chosen (this is fleshed out further in the points below). It would be disappointing if this valuable treatment is rejected by NICE purely because of modelling difficulties.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

In relation to whether the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, the clinical and cost effectiveness evidence summaries rely on a couple of assumptions that NICE have made:

1. That cetuximab did not affect survival.

The control arm in the trial was FOLFIRI and Cetuximab - as clinicians do not use with Cetuximab routinely in the UK, NICE have assumed in their assessment that the response to FOLFIRI would be the same as the response to FOLFIRI in combination with Cetuximab. The drug manufacturer made the assumption that Cetuximab added survival benefit and corrected for this which is a sound approach. There is a lack of clear consensus in the UK around the addition of Cetuximab to Irinotecan or FOLFIRI in 2nd/3rd line mCRC patients as opposed to using the chemotherapy agent(s) alone. The drug manufacturers felt that their hands were tied re using Cetuximab in the control arm as this was an international consensus, and resulted in their trial not representing standard UK practice. It would have been impossible to recruit successfully to an adequately powered UK-only randomised controlled trial in a timely manner. Given the complexities around the control arm, we would recommend that NICE would consider this to be a grey area and lean in favour of the patient.

2. That Lonsurf and FOLFIRI are equivalent and therefore it's reasonable to perform the cost effectiveness of the novel doublet against either.

This assumption is considered to be incorrect. Bowel Cancer UK's medical advisors have informed us clinicians would opt for FOLFOXIRI or FOLFOX/FOLFIRI as first or first/second line treatments. Clinicians would NOT opt for Lonsurf before exhausting conventional oxaliplatin and irinotecan based treatments. If NICE were to lean towards recommending the novel doublet in the fourth line, this would be a huge disservice to patients given the clearly documented worse post-progression survival of patients with BRAF V600E mutant metastatic CRC. From clinical audit data (eg West of Scotland) representing real world UK data as well as the pivotal trials, many patients are not fit for second line systemic anti-cancer therapy and only a small minority receive third line treatment. Consequently, if NICE recommended Lonsurf prior to the novel doublet it would result in very few patients actually receiving it given the attrition of alive and

sufficiently fit patients. Furthermore, the RECOURSE pivotal trial for Lonsurf did not include comprehensive data on BRAF mutant status, so the committee have made the assumption that a patient with BRAF mutant disease will respond in the same way as those with RAS wild type disease which is implausible to those of us who treat metastatic colorectal cancer. If one were to try and make a hypothesis on the response of BRAF mutant patients to Lonsurf in the absence of data, we would strongly recommend modelling the patients who have a very small chance indeed of responding to Lonsurf (i.e. those with progressive disease on all prior lines of therapy).

Are the recommendations sound and a suitable basis for guidance to the NHS?

The provisional recommendations are not considered to be sound and a suitable basis for guidance to the NHS. The patient group for this appraisal is a very small sub type of bowel cancer patients (8-10% of the total population) and face a very poor prognosis – with survival often less than six months. If 8-10 patients in every 100 with mBRAF have first line treatment and optimistically 40-50% are fit for second line treatment, then this would mean that at the most only 3-4 would be able to receive the novel doublet. The increase in overall survival seen with encorafenib and cetuximab (median OS increased from 5.9 to 9.3 months) is clinically and statistically highly significant and is the only trial thus far which has shown any advance in this patient group. It is also a very small number of patients per year – from modelling in Glasgow it was to be roughly 20 patients per annum for the 5.5 million population of Scotland. Given this orphan group with extremely poor prognosis, we would have hoped for a much more liberal input to the modelling – in particular around the grey areas e.g. the standard arm is not the standard of care in the UK.

It is also worth noting that this is the only licensed BRAF mutant metastatic colorectal cancer treatment available and this is already being widely adopted around the world. Hence, any future treatments will have Cetuximab and Encorafenib as their control arm. If this doublet were to be rejected by NICE, then it will not be able to be used as a comparator arm for future appraisals in the UK and further prevent access to targeted treatment for this patient group.

Finally, patient tolerance of their treatment regimens and their quality of life are hugely important. It is notable that, in the BEACON CRC trial, the adverse events from therapy were lower with Cetuximab and Encorafenib than with the control arm, as was the proportion of patients who had to discontinue their therapy due to treatment-related toxicities.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Yes

Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

This treatment should be available on the nhs to all cancer patience that need it. People are dying when there is a treatment that can help prolong life

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Proposed date for review of guidance The review needs to be bought forward to save lives	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
It seems absolutely ridiculous that these drugs are not being offered to bowel cancer patients when the evidence suggests they can have such a positive impact and potentially increase their life my years. The fact that money is placed as a much higher priority than people lives such as those of my cousin - a young mum is disgraceful.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
It is a disgrace that this drug is not being approved for those who need it. It is my understanding that the data is incredibly strong and that there are cases of patients surviving in excess of 3 year having undergone this treatment. The drug has already been approved in Europe and America, and in the UK you are condemning people to an early death. Those people are Mothers and Fathers. Think of the impact of having 3 more years with their parents will have for those children. These people are brothers, sisters, friends. They deserve to have more time and you have the ability to grant them that. This should never be about money. It is about humanity. If you decide to leave these people to die an unnecessarily early death because it costs too much money, may God have mercy on your soul.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life. Has all of the relevant evidence been taken into account? Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy. Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? A separate study has shown that 75.9% of patients received some benefits to these drugs as compared 31.2% with the usual drugs and that some younger patients are in complete remission.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Has all of the relevant evidence been taken into account?

There seems to be a lot of uncertainty with the evidence.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Appear so.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Seems to be a lot of uncertainly with comparisons.

Recommendations

How reliable is indirect comparisons for this treatment? What is the element of assumption versus quantitative evidence of effectiveness? It is concerning a drug combination that will extend life so it is worrying assumptions are part of this decision making.
In regards to cost effectiveness, life extending treatments for people living with cancer surely should be made on an individual basis in relation to quality of life and pre-existing comorbidities influencing effectiveness.

Price

Comparisons with other treatments would have been useful here.
Also balancing the cost of symptom control and palliative care costs in terms of staff, equipment and other resources such as counselling, and bereavement care against this drug combination would be useful. For younger fit people living with this cancer, returning to the work force, not having to claim benefits or needed further support could be taken into consideration.

Committee discussion

Encorafenib plus cetuximab is an innovative treatment for BRAF V600E mutation-positive metastatic colorectal cancer

The benefits here of the lack of side effects as there are from chemotherapy are very positive. Also by using new treatments further research is possible. There is an unmet need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer Starting new treatments of complex cancers will surely lead to further research opportunities to allow direct comparison and investigations into effectiveness to take place, People would welcome an effective treatment option for BRAF V600E mutation-positive metastatic colorectal cancer Having such a marked improvement in symptoms time for the individual but also society and the economy. Further exploration of modelling overall survival for encorafenib plus cetuximab is needed Further exploration of modelling overall survival for encorafenib plus cetuximab is needed The cost effectiveness of encorafenib plus cetuximab compared with trifluridine–tipiracil would be very uncertain All the comparisons are uncertain so how can decisions be confidently made?

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
As the document states - if this were available and used earlier it gives people back life - years of it rather than the time from diagnosis to death being a painful 7 month slog through chemo that has less than a 10% chance of successfully extending life	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
The evidence of effectiveness has been proven and with the drugs being given approval in the EU and the US, we should do the same here in the UK, regardless of cost effectiveness arguments	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

The drug cost does not appear to be prohibitive, the CDF website states the fund allows 'Access to promising new treatments, via managed access arrangement, while further evidence is collected to address clinical uncertainty'. It seems that encorafenib, having gained market authorisation may fit this criteria, so therefore should be recommended for use whilst further data is collected. Otherwise is the opportunity missed to reach a scientific conclusion regarding it's efficacy?

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendation not to authorise use of encorafenib rests partly on the fact that comparators used are not part of normal clinical practice in the NHS. Are the comparators used in the BEACON trial normal practice in other countries , as the trial was a global multicentre trial? If so why would this lead to the results being discounted ?
The clinical experts suggest encorafenib + cetuximab it is the only treatment to date that demonstrates both a clinically meaningful and statistically significant difference in terms of overall survival in this patient population in a phase 3 trial.

Committee discussion

There is an unmet need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer

Metastatic colorectal cancer with a BRAF V600E mutation is a rare type of colorectal cancer. It is that rare -around 15% of people with various cancers have this gene that makes their cancer chemo-resistant ?

Proposed date for review of guidance
This is a long review date for individuals with this disease, many of whom may not survive for three years.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The research regarding bowel cancer indicates a much younger population are being diagnosed with this cancer. There is a general and incorrect view that bowel cancer mostly impacts the older generation, age must be taken into account particularly for those younger patients whose treatment options are limited and if this recommendation is followed, would be significantly impacted upon.

Has all of the relevant evidence been taken into account?

Further evidence is required to address the clinical uncertainty. The evidence highlights the combination of drugs extend life and is the only options available, however there is not an alternative currently being trialled and therefore there will be this cohort of patients without an effective treatment plan.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Again, the reason this is not being used is mainly due to the cost of the drug combination. As mentioned, this cohort of Braf gene is a smaller cohort but one that should not be side-lined and live in fear of having no treatment available to them due to the costing. Within 2020, there has been a significant amount of money spent on the Covid pandemic, building hospitals that have not been required, this has taken finances out of trials and treatment for cancer patients whom desperately this to live life to their fullest. I would not agree this is suitable guidance to the NHS given there is evidence this combination extends life.

Recommendations

This recommendation is not intended to affect treatment with encorafenib plus cetuximab that was started in the NHS before this guidance was published.

his is unfair for those patients whom applications are in progress. This is likely to have a negative impact on the psychological wellbeing of these patients.

Clinical trial evidence shows that encorafenib plus cetuximab increases how long people live compared with FOLFIRI plus cetuximab or irinotecan plus cetuximab.

This evidence highlights the difference the combination of these drugs has on ones' life.

But the cost-effectiveness estimates are higher than what is normally considered a cost-effective use of NHS resources, so it cannot be recommended for routine use in the NHS.

As a tax payer, I should have some say in relation to how the money is spent, it is a sad country we live in to decide the length of life based on finances. The cohort of cancer patients with this gene is up to 15% which would reduce the spenditure.

Collecting further data is unlikely to address the clinical uncertainty.

This is contradictory from the comment the combination of the drugs increases length of life.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The trial seems to have largely ignored the under 60's where response to the new drugs and recovery from the cancer may be expected to be more pronounced and therefore more beneficial for both patients and families.

Has all of the relevant evidence been taken into account?

I do not believe that the conclusions fully take into account the particular success rate for the treatment of metastatic colorectal cancer, which shows an average overall benefit to 75% of those treated and the likely increased benefits to those aged under 60.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I think a cost comparison with established drugs should be properly shown and weighted against their relative effectiveness although I do not believe that such life saving drugs should be restricted purely for reasons of expense, especially when other 'cost-benefits' are not taken into account (e.g. cost saving on other drugs/treatment, quality of life, mental welfare of patient and family, etc)

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, I cannot accept that a relatively low cost treatment showing an overall success rate of 75% should be denied to those suffering from this form of cancer, nor that younger patients, who have more to lose, have been substantially excluded and are not to be given this new drug, or at least given a chance to participate in a wider ranging trial. This would seem to be inequitable and possibly ageist.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	

Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? By using an average age of over 60 you are being discriminating towards young patients and denying these young patients their chance of life-saving drugs. It has been shown that for younger patients, the quality of life would be greatly improved with the use of Encorafenib plus cetuximab opposed to chemotherapy.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No Has all of the relevant evidence been taken into account? Not sure Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No Are the recommendations sound and a suitable basis for guidance to the NHS? No These drugs need to be approved to be used on the NHS. They are already used all over Europe and the US as they have been proven to work and give many, many people a longer life. To not approve them due to money is disgusting. You can't put a price on people's lives. How come all these other countries manage to afford them? These kind of bad desicions are why the UK is soooo behind other countries when it comes to cancer treatment!	

Name	[redacted]
Role	

Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Refusal to provide a known supportive therapy potentially denies an individual of their human right to life for as long as possible.
Particularly when there are limited options for treatment for the BRAF mutation.

Has all of the relevant evidence been taken into account?

Would question whether consideration has been given to the potential savings from this treatment, in relation to other medical costs in terms of Pharmaceutical medicines to deal with side effects eg neuropathic damage, antisickness medication, painkillers, together with potential tangible reductions for inpatient and out patient care.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Would question whether consideration has been given to the potential savings from this treatment, in relation to other medical costs in terms of Pharmaceutical medicines to deal with side effects eg neuropathic damage, antisickness medication, painkillers, together with potential tangible reductions for inpatient and out patient care.

I also question whether sufficient significance has been placed on this treatment meets an unmet need for treatment and being a step change in treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - this treatment should be available on the NHS given the unmet need for treatments for BRAF V600E and the step change it provides in treatment.

The appraisal document notes that this treatment is less toxic and more manageable than the two most prevalent alternatives (3.2; 3.9; 3.31). This has the potential to reduce other medical costs in terms of Pharmaceutical medicines to deal with side effects eg neuropathic damage, antisickness medication, painkillers, together with potential tangible reductions for inpatient and out patient care.

In addition, the psychological impact (3.2) of having the potential of an additional life expectancy and or reduction in side effects is immense although perhaps not quantifiable. However, again has the potential to reduce the burden for NHS support services in relation to counselling and medication.

The current availability of this treatment is only after one or two alternative chemotherapy regimes have been completed. This may mean some do not survive to take advantage of this treatment reducing the costs and the percentage of potential recipients. On the other hand if it was available as a first line of defence then the costs of the alternative routes must reduce the total cost of the encorafenib/cetuximab treatment over the period of treatment (3.3; 3.4; 3.6).

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I urge NICE to reconsider the recommendation on this. The NICE recommendations should be based on science, not money and there is clear evidence the combination of these drugs works. We can't be the only country in the developed world where people die young despite the fact that there is a clinically proven clear drug that can prolong their life.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account? It is based upon age discrimination – it was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life. Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life-long chemotherapy Are the recommendations sound and a suitable basis for guidance to the NHS? Please reconsider your refusal to recommend Encorafenib in combination with Cetuximab for patients with metastatic colorectal cancer with a BRAF V600E mutation	

Name	[redacted]
Role	
Other role	

Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

A growing trend is occurring in younger people with BRAF V600E mutations.

Has all of the relevant evidence been taken into account?

I am unsure of all of the evidence used. However the evidence used points towards this drug being beneficial, so the evidence suggests that it should be used.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No. The evidence supports the use of this treatment. What is ridiculous is that I personally have had 20 rounds of "useless" chemotherapy treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The recommendations are full of contradictions and should not be used as guidance to the NHS. The recommendation based on the evidence, goes against the positive evidence it can help improve and prolong BRAF V600E patients lives

Recommendations

Encorafenib plus cetuximab is not recommended, within its marketing authorisation, for treating BRAF V600E mutation-positive metastatic colorectal cancer in adults who have had previous systemic treatment.

This contradicts the results and is the ONLY proven treatment for treating people with BRAF V600E mutation positive metastatic colorectal cancer in adults. It is the only recommended treatment for this type of mutation.

This recommendation is not intended to affect treatment with encorafenib plus cetuximab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

This contradicts the previous section in 1.1. If it is not recommended, then surely these lucky early access scheme participants would not be able to access the drug combination any more. As a BRAF V600E colorectal patient that has undergone 4 major open surgeries and 20 rounds of chemo in 3 years, this is my only life extending option left. It clearly shows some positive impact on the patients on the early access scheme.

Encorafenib plus cetuximab meets NICE's criteria for being a life-extending treatment at the end of life. But the cost-effectiveness estimates are higher than

what is normally considered a cost-effective use of NHS resources, so it cannot be recommended for routine use in the NHS.

This is ridiculous, as a stage 4 colorectal patient that in 2017 had a bowel resection + 7 days in hospital, 3 months of FOLFIRI + Cetuximab, A 50% liver resection + 7 days in hospital, 3 months of CAPOX chemotherapy. In 2019 1 lung/pleura/laser resection + 7 days in hospital, 6 months of CAPOX. In 2020 another lung/rib resection. The costs incurred already would be completely wasted if this drug is considered "non cost effective". It would would mean all NHS effort and spend to date has been a waste of time. To stop now is completely insane.

Price

The list price of encorafenib 75 mg is £1,400 for 42 capsules (excluding VAT; BNF online accessed August 2020). The company has a commercial arrangement. This makes encorafenib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended

As more of the drug is issued, this should lead to increased production and lower costs. Also, as an organisation, you have the power to negotiate a better price for these drugs.

Committee discussion

The committee noted that because the treatment is not a chemotherapy, it is transformative for people's quality of life. The committee concluded that encorafenib plus cetuximab is an innovative treatment for V600E mutation-positive colorectal cancer.

If it is an innovative treatment that transforms peoples lives, why is not being given as a treatment? I would welcome this treatment as it would significantly improve my life/life expectancy.

The clinical experts explained that there are currently no effective treatments for this type of colorectal cancer and encorafenib plus cetuximab represents a step change in treatment. The committee concluded that there is an unmet need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer.

f this represents a positive treatment and is the only drug available then it would be criminal to deny patients like myself access to the only drug that has been shown to extend life in BRAF V600E patients. If there is an unmet need, then surely this is the only current way to meet it.

Metastatic colorectal cancer is a progressive condition that affects survival and quality of life. The patient experts highlighted the psychological effects of a diagnosis of metastatic BRAF V600E mutation-positive colorectal cancer and the lasting adverse effects of current treatments such as neuropathic damage. The patient experts explained that their cancer responded quickly to triple therapy (encorafenib plus binimetinib and cetuximab) and this was life-changing, whereas they saw little to no response on previous treatment. They noted that their quality of life improved enormously because the adverse effects are manageable compared with other treatments. The committee concluded that both patients and healthcare professionals would welcome an effective new treatment.
As a patient that has undergone 4 major surgeries, 1 bowel, 1 liver 2 lung + 20 rounds of chemo (including feeling neuropathic damage), it seems insane based

on the the response rates and improved quality of life that this drug is not being approved. I would be grateful of receiving this treatment as my treatment options have ran out.

Encorafenib plus cetuximab is not recommended for use in the Cancer Drugs Fund

As someone that needs these drugs, it is crazy that the spend on my treatment has probably exceeded £500,000+ on the NHS. If this drug is not funded then you may as well put people like myself down on diagnosis. I have fought for 3.5 years to stay alive and to be told that the only drug combination that has any effect is not being funded is a disgrace. Are you going to tell people with my condition not to bother fighting? Not to bother trying to stay alive to push forward medical progress?

Proposed date for review of guidance

This is a very long time to review the guidance. This should be reviewed immediately. For patients like myself, 3 years is a too long.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

There is a strong age descrimination as the study was based on an average age of 60 ,denying younger patients access.

Has all of the relevant evidence been taken into account?

This combination of drugs can improve quality of life over and above life long chemotherapy.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Another study has shown three quarters of patients were helped with these drugs compared with a third with usual drugs.

Are the recommendations sound and a suitable basis for guidance to the NHS?

America and Europe have approved the use of these drugs. Chemotherapy is an expensive and very invasive treatment for life long use.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This treatment should be trialled in England as recommended by the European Union	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Please PLEASE reconsider the decision about the price/budget of this life saving project?? This can actually bring hope and normality back to patients without this mutation , many of whom would be able to return to work and once again become contributors to hmrc!!	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Given the amount of money and effort for the research, and given that the trial was successful, NHS should offer this therapy, people with V600E rare mutation have their right to get this treatment.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? How very cruel for a young man to realise that a drug is available to extend his life but he cant have it due to expense. He is [redacted] years old with [redacted] [redacted] who want to save their daddy Has all of the relevant evidence been taken into account? Not for young people Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Cost seems to be a priority over lives Are the recommendations sound and a suitable basis for guidance to the NHS? Funding should be there to help young people	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Don’t put a cost to someone’s life. Make it free on the NHS . Do the right thing. Save lives. Don’t make decision that’ll end in deaths. Stop playing god. Find a way.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	

Notes	
Comments on the ACD:	
Please reconsider your refusal to recommend Encorafenib in combination with Cetuximab for patients with metastatic colorectal cancer with a BRAF V600E Mutation. This drug has been approved in Europe and America. There has been study's to show 75.9% of patients received benefits to these drugs compared with 31.2% with the usual drugs.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No Has all of the relevant evidence been taken into account? We were disappointed read the outcome of the NICE Technology Appraisal of Encorafenib and Cetuximab for colorectal cancer patients with a BRAF V600E mutation. We would like to make the following points when considering the context of the BEACON trial and the management of patients with BRAF V600E mutations specifically. 1. BRAF V600E mutation and its implications on survival a. As the committee is aware patients with BRAF V600 mutation represent approximately 8% of patients in a first-line disease setting have a poor prognosis with standard chemotherapy agents. Vanderbosch et al performed a pooled analysis of 3063 patients in first-line CAIRO, CAIRO-2, COIN and FOCUS trials and identified 250 BRAF V600E mutant patients with an OS of 11.4 months from commencing first-line chemotherapy without an EGFRi versus 17.2 months in wild-type patients. Subsequently Seligmann et al analysed 2530 patients from the UK FOCUS, COIN and PICCOLO trials. In the context of second line treatment this study demonstrated that BRAF mutant patients had worse OS in 2nd line setting compared with non-mutant patients, whether they received chemotherapy (HR 1.91 (1.36-2.69), p<0.001) or not (HR 1.44 (1.22-1.84), p=0.004). Survival following progression on first-line chemotherapy of BRAF V600E patients was significantly reduced in FOCUS and COIN trial patients (3.2 months vs. 8.6 months, HR = 1.72 [1.35–2.19], p < 0.001). In patients fit enough to proceed with 2nd line chemotherapy in a clinical trial the PICCOLO study observed an OS of 6.7 months for BRAF V600E vs 10.2 months for wild-type patients . b. Analysis of this data therefore suggests that the prognosis of BRAF V600E patients is poor with survival on average of approximately 1 year from initial presentation. Given this short Overall Survival from initial presentation it is likely that many with BRAF V600E mutations patients do not survive long enough to receive 3rd line chemotherapy and that available 2nd line standard chemotherapy	

is of limited benefit. Therefore this small cohort of patients are a niche group that are in need novel targeted treatment in the 2nd line setting.

2. BEACON study design

a. It would not have been possible to perform an adequately powered UK-only RCT in the BRAF V600E patient sub-group in a timely manner and therefore international collaboration was required to undertake a study in this disease setting. Given the available data described above a trial in a 2nd and 3rd line disease setting was optimal to maximise patient recruitment given the limitations of standard chemotherapy. Many clinicians prefer to treat these patients with a combination of Oxaliplatin, Irinotecan and 5FU (FOLFOXIRI or FOLFOX / FOLFIRI if not fit enough to receive the triplet therapy) in a first-line setting given some clinical data suggesting improved survival, and in part due to the data demonstrating very poor survival after progression on first-line treatment.

b. At the inception of the BEACON trial there was uncertainty regarding whether BRAF V600E mutation was predictive of lack of benefit from EGFRi targeted treatment. The 1st line CRYSTAL study suggested BRAF V600E was prognostic but not predictive whilst the 2nd line PICCOLO trial suggested BRAF V600E was prognostic but potentially also predictive of lack of benefit from EGFRi treatment. European Society of Medical Oncology (ESMO) guidelines recommend irinotecan based chemotherapy (Irinotecan or Irinotecan/ 5FU) and an EGFRi as 2nd/ 3rd line treatment option for RAS wild-type metastatic colorectal cancer.

c. It was therefore reasonable in an international context to include Cetuximab in the standard treatment arm given the uncertainty over treatment outcomes. It was also reasonable, given the available clinical data to recommend either irinotecan/ cetuximab or irinotecan/ 5FU/ cetuximab as standard treatment options. These decisions will have enabled trial recruitment internationally although we recognise they have caused the NICE committee some difficulties in data interpretation.

3. Consideration of BEACON standard treatment arm in context of NHS practice

a. Irinotecan vs. irinotecan/ 5FU comparison - The FOCUS trial assessed a strategy of single agent 5FU followed by single agent irinotecan which it compared with a variety of other combinations and sequences of 5FU, Irinotecan and Oxaliplatin. One strategy compared the standard arm with first-line 5FU followed by second-line 5FU and Irinotecan (FOLFIRI) therefore providing an indirect comparison of 2nd line single agent Irinotecan and FOLFIRI. The comparison demonstrated survival of 13.9 months vs. 15.0 months (HR 0.91 (0.79-1.03), p=0.16). Although there was a trend favouring FOLFIRI it did not reach statistical significance in a group of patients with unknown mutation status.

b. NICE NG151 reviewed data regarding molecular biomarkers in colorectal cancer and concluded that BRAF V600E should be assessed in all patients. This decision was based on a pooled analysis of studies which demonstrated that presence of a BRAF V600E mutation predicted failure of EGFRi treatment and poorer progression-free and overall survival compared to BRAF wild-type patients.

c. Given the data from the FOCUS trial, the NG151 biomarker analysis and the poor survival of BRAF V600E patients it is highly unlikely that the different options for standard treatment within the BEACON trial would be associated with a clinically significant difference in patient outcome. It is also very unlikely that these options would produce significantly different outcomes to standard NHS treatment options.

4. Second and third line comparators

a. The standard comparators will depend on whether Encorafenib / Cetuximab is considered at the 2nd or 3rd line stage. The preference based on the discussion above would be for it to be given in the 2nd line setting after triplet treatment. The comparator at this stage would be Lonsurf. If only 1st line FOLFOX was given then

the comparator would be FOLFIRI (or vice versa). If the Encorafenib / Cetuximab was given in the 3rd line setting (less likely), then the comparator would be Lonsurf. There are some important caveats when considering the BEACON trial in comparison with the RECOURSE study which assessed Lonsurf. The BEACON trial included patients in a 2nd or 3rd line treatment setting but patients who had more than 3 prior lines of treatment were not eligible for the trial. In contrast, in the RECOURSE trial approximately 60% of patients had received 4 or more prior lines of treatment. The RECOURSE group had incomplete data regarding BRAF mutation status but have presented some data in abstract form. Of 800 RECOURSE patients 116 (15% of trial population) had BRAF V600E status assessed of whom 8 (1%) had a mutation. Therefore the vast majority of patients in the RECOURSE trial either had wtBRAF or did not have their BRAF status assessed. It is therefore very difficult to compare this trial to patients in the BEACON tral who all had mBRAF. Data from the same study showed expected proportions of patients with KRAS mutations. It therefore seems likely that patients with BRAF V600E mutations are under-represented in the RECOURSE study given their poor prognosis.

References

- Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN and FOCUS studies. Vanderbosch S, et al., Clin Cancer Res. 20(20): 5322–5330, 2014.
- Investigating the poor outcomes of BRAF-mutant advanced colorectal cancer: analysis from 2530 patients in randomised clinical trials. Seligmann J, et al., Ann Oncol. Vol 28 (3), p562-568, 2017.
- Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Seymour et al. Lancet Oncol; 14: p749–59, 2013
- 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. Van Cutsem E., J Clin Oncol. May 20;29(15): p2011-9, 2011.
- Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Van Cutsem E., Annals of Oncology 25 (Supplement 3): iii1–iii9, 2014.
- Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. Seymour MT, et al., The Lancet, Vol 370, Issue 9582, p143-152, 2007.
- https://www.nice.org.uk/guidance/ng151
- Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. Mayer RJ, et al., N Engl J Med 2015;372:1909-19
- KRAS and BRAF gene subgroup analysis in the phase 3 RECOURSE trial of TAS-102 versus placebo in patients with metastatic colorectal cancer. Hochster H, et al., Annals of Oncology, 26 (S4): iv108- iv116, 2015

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

As we have described in our previous answer we are concerned that some of the assumptions made in interpreting the clinical data are not valid or are uncertain. These include:

1. Irinotecan vs. Irinotecan/5FU vs Ir/ Cetuximab vs Ir/ 5FU/ Cetuximab - the available evidence suggests that in BRAF V600 patients the efficacy of these regimens used in standard NHS practice or in the BEACON trial is likely to be

extremely limited. It is unlikely that any of these regimens would produce significantly improved outcomes compared another. We would draw attention to data from the FOCUS and PICCOLO trials, pooled analyses of UK and European randomised trials related to BRAF V600E, as well as the NG151 biomarker analysis.
2. 3rd line comparisons - we would strongly urge the committee to appraise Encorafenib and Cetuximab in a 2nd line treatment setting. Comparisons with the RECOURSE trial and Lonsurf use are uncertain and may not be valid given the significant differences in the trial populations re previous treatment and the fact that BRAF V600E patients are likely to be significantly under-represented in the RECOURSE trial population. As discussed in the answer to the "relevant evidence" question we would also note the very poor prognosis of BRAF V600E patients and likelihood that many patients would not be candidates for 3rd line treatment due to clinical and/ or biochemical deterioration. Although the BEACON study recruited patients in both the 2nd and 3rd line treatment settings approximately 65% were in the 2nd line setting.
3. We are aware that details of the modelling and cost-effectiveness assessments have not been made available due to commercial confidences but this makes it difficult to comment regarding this aspect of the consultation.

Are the recommendations sound and a suitable basis for guidance to the NHS?

We strongly believe that Encorafenib and Cetuximab should be an option for patients with BRAF V600E mutant colorectal cancer and hope that the committee will be able to review the comments and data provided and re-assess the decision.

As described we hope we have provided further context for the analysis of the BEACON trial within NHS practice. Encorafenib and Cetuximab have clearly demonstrated clinically and statistically significant differences in outcomes for a group of patients who have extremely poor outcomes with standard chemotherapies, and for whom EGFRi treatment combined with chemotherapy does not appear to be useful. Specifically, conventional 2nd line chemotherapy is of little use in these patients with a very poor prognosis. The survival advantage observed in the BEACON trial relates to the activity of Encorafenib and Cetuximab rather than any subsequent treatments which will only have been given to a very small proportion of patients in the trial. Patients with mBRAF represent a very small cohort of patients (likely less than 5% of patients assuming only 50% of 1st line patients are fit enough to receive 2nd line therapy). We accept there are modelling difficulties in terms of comparators, but we wouldn't want this factor to be the reason why this valuable treatment is rejected by NICE. We appreciate that for confidentiality reasons the details of the financial modelling are not available for review. We however hope that re-appraisal, in light of the clinical data we've presented, and further discussion financial models with the companies involved, may be result in a positive outcome for our patients.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	

Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? I don't think there's anything unlawful, but the cited studies don't reflect the results in younger patients Has all of the relevant evidence been taken into account? I am not qualified to comment Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? I am not qualified to comment Are the recommendations sound and a suitable basis for guidance to the NHS? Ultimately, it is for the NHS to decide, but I know this drug gives a lot of comfort and hope to people. Hi. I'd be really grateful if you could please reconsider your decision on this. I know it can offer huge increases in quality of life to patients who otherwise would have to undergo chemotherapy, and that it is more effective than other proposed drugs. Thanks for your reconsideration.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
It is heartbreaking to see cost blocking this treatment which demonstrably not only prolongs life but significantly improves quality of life. As a bowel cancer widow I despair for those suffering now and in the future.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Earlier this year, my [redacted] year old sister died from metastatic bowel cancer. Her particular mutation means that the drugs in this article would not have benefitted her. I cannot imagine a more desperate situation than drugs which have been shown to prolong and enhance quality of life being denied to a person in a similar situation. NICE and the NHS are creating a two tier health service in denying these treatments to those for whom self funding is not an option. I implore you to reconsider this decision and provide proven treatments to those who will otherwise be facing certain and rapid decline.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
My cousins husband is desperately ill and this treatment will severely increase his chances of survival. Please make it accessible through the NHS	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
My [redacted] has recently died from this terrible disease, she leaves a [redacted] year old daughter and a family who will never recover from this terrible loss. She suffered greatly and because this treatment was not licensed in this country time was lost, through protocol. Even though she was the ideal candidate, because of the hoops that had to be gone through by the time treatment had been granted, she was too ill to receive it. I feel so angry that she was denied the chance to spend more time with her young daughter, husband and family who are totally devastated and pray that no other family will be robbed of precious time due to this terrible cancer. if NICE are saying that cost is the problem why isn't more being done to negotiate with the drug companies who are making millions from this product which costs little to produce and compare this with the cost of chemo which is ineffective and the huge cost to family life. I pray that others do not have to suffer as we do.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

NICE states that only indirect assumptions can be made as to efficacy yet all available data points to increased lifespan and benefits. Given the limited options for many relevant patients outside of chemotherapy and all the life limiting side effects that brings, could NICE instead look to partially fund this drug for a limited time in order to itself build up a better dataset around efficacy.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
. These drugs give people time and give people more life with their loved ones. In some cases they have helped to get rid of the cancer (it is known as an incurable cancer). The average person with metastatic bowel cancer with the BRAF mutation has 7 months from diagnosis until they die, because of its severity. This set of drugs is keeping people alive for years. Sadly a friend of mine was due to start taking them but died first.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I don't believe the extension of a life should be measured against cost effectiveness. My [redacted] recently died with this disease, and who knows whether or not some ground breaking cure may have been found in the extra time she could have been given. Notwithstanding the above, that extra time, even if it was only a couple of months, would have given her the opportunity to put her affairs straight. As it was, she was given 3-6 months to live, but that quickly turned into less than a month. I know there is never enough time, but this seemed cruel.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

. This should be available for ALL cancer patients, in ALL countries There's is strong data showing it's success Perhaps if more was available my father would have survived this , we lost him aged [redacted] Post code lottery is unjust!!

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes. This type of cancer affects only a small proportion of mainly younger/middle aged women with metastatic bowel cancer. To deny this treatment discriminates against this group of women.

The mutation is known to affect young women primarily and its omission from availability obviously discriminates against age and gender. This is unfair.

Has all of the relevant evidence been taken into account?

The consultation indicates the Committee did not consider there was sufficient evidence to endorse the use of the treatment yet accepts there is no evidence to indicate the treatment does not meet the criteria for a life extending treatment: "The committee concluded that encorafenib plus cetuximab met the criteria to be considered a life-extending end of life treatment". Given this and the absence of other treatments for this BRAFV 600E mutation and the significant benefits described in the evidence whereby cancer patients find "their quality of life improved enormously because the adverse effects are manageable compared with other treatments", the treatment should be made available for the very small group of cancer sufferers.

The evidence has been discussed, but the conclusions and recommendations are biased towards cost rather than efficacy.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No they are not. From the consultation it appears that the clinical effectiveness is most advantageous in so far as nearly 40% of patients experiencing this mutation and having the treatment concerned. had their lives significantly extended. The cost must be in proportion to the number of patients affected; this number is known To be quite limited and, therefore, the interpretation of the cost effectiveness is not a balanced reflection of the facts.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. I believe the treatment should be made available to oncologists to prescribe as they see fit to this small group of cancer sufferers. The cancer is a particularly aggressive form of colorectal cancer and treatment has the potential for significant improvements for the quality of life of sufferers.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The recommendations would appear to be primarily cost based; no regard is being paid to the age group (young) predominantly concerned and, furthermore, the oncologists will not be able to choose to offer the known advantages of the treatment to those who are fit and without underlying complications who would benefit most.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
BRAF V600E mutant patients benefit from encorafenib and cetuximab. It is important that this is an option for our patients. Please consider further negotiation with drug companies involved to open this option for our patients.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Recommendations This decision is unfair to the patients with BRAF V600E mutation-positive colorectal cancer, who face no alternative targeted treatment. Recommending the Encorafenib plus cetuximab treatment would give hope to the few patients of this rare mutatation at this stage of care, for a better quality of life without the effects of chemotherapy, and has shown remarkable reduction in number of tumours in some cases.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	

Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Age NICE's decision to not fund the drugs discriminates against younger patients. The study uses patients where the average age is 60-62 and this therefore denies younger people e.g. aged 30-40 a chance of life saving drugs. A few people in the study saw their tumours shrink away to nothing and younger patients might be those who have successful outcomes as they will probably tolerate the treatment better than older patients. These patients will probably have young families and would also benefit enormously from a much greater quality of life by having oral medication instead of regimens of chemotherapy/ radiotherapy. There are currently no licensed treatments available specifically for patients with tumours with BRAFV600E mutations and given the poor prognosis for these patients they deserve this opportunity (particularly the young). The trial shows the first ever significant advance for this group of patients using a treatment that is easily administered and tolerated. This treatment has already been approved in both the USA and Europe and UK patients deserve an equal opportunity.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Having read this paper I generally feel those with this mutation despite all of the grounds above are being disadvantaged simply by being citizens of the UK. Other countries are successfully using this combination and this appear to be a cost decision. No cost can be put on the life extension of another human. More and more young people are being diagnosed after contact with NhS professionals who have failed to send for the correct screening, screening that would have helped at much earlier stages. Negligence is then life changing for the young people, who are mothers and fathers of young children themselves. The impact on not backing this combination to offer life extending treatment impacts not just in them but all of those around them. Their children, partners etc. Children are loosing their parents at an age which will emotionally scar them forever. The cost and impact to felt further down the line by the NHS. The combination tried and tested does work. Has all of the relevant evidence been taken into account?	

don’t think it has. There are people who are trialling these drugs that can show they work, they give extra time to families. This is surely evidence enough. The extended quality of life of priceless. These people with this mutation need hope. It baffles me how decisions are made with public spending how some things are backed and other are not. On what appears to be more about cost effectiveness than anything else. We do lots to help others in hopeless situations to help prolong and extend life.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

don’t feel they are. What would be the likely cost implications for the small numbers who have this mutation. Would all who have it even except it? So many cancer patients refuse treatment at all so is there any real cost analysis based on current numbers of patients?

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations to proceed based on evidence from those trialling these drugs should be the main consideration.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I feel very strongly given the evidence provided that this drug should be made available to those patients who would respond best - i.e. those who are relatively young and especially those who are otherwise for and healthy. There should be differentiated criteria for treatment based on other relevant factors. A standardised response such as that set out in this recommendation does not reflect the different circumstances of each patient who presents with this mutation.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	

Yes discrimination on the grounds of age. There is an increase of younger people with bowel cancer and BRAF V600E mutation which needs to addressed and investigated further.

Has all of the relevant evidence been taken into account?

Currently there are no effective treatments for this type of cancer/gene mutation, but as stated these two drugs represent a step change in treatment. The committee agreed patients and healthcare professionals would welcome an effective new treatment. Results from August 2009 showed that the two drugs combined increased overall survival. I feel it is a contradiction saying these treatments prolong life but are not available for use on the NHS.
These two drugs are an innovative treatment for BRAF V600E mutation positive metastatic colorectal cancer agreed by patients and clinical experts. If the committee is aware there are no other treatments that offers extra time and targets for other treatment options in the future , surely another plus for these drugs to be approved.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Could these drugs be produced more economically if produced on a larger scale or by another drug company. This particular drug company has a commercial agreement but is there no other companies that could tender for costings? The committee agreed to welcome an effective treatment, if so are the committee going to veto every new treatment on a financial basis?

Are the recommendations sound and a suitable basis for guidance to the NHS?

These drugs would give people of improved outcomes as clinical experts agree these two drugs could be used when no other active treatments available so why can the treatment be given on an individual basis after assessment of well being of each patient

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Stage 4 patients should not be penalised with shortened life due to funds not being allocated. Especially when this medication has/ is used in other countries and has been proven to work. When a treatment is avaliable then patients have a right to access it.	

Name	[redacted]

Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
How can an effective proven drug be denied when it is needed on the basis of cost? This is not a good enough reason for it to be denied.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

yes - although the comment about the SOC arm within the trial not being relevant to the UK is not a reason to reject the regime.
This was a global study and NICE must factor for that

Treatment for BRAF mutated colorectal cancer (especially post oxaliplatin and irinotecan based chemotherapy) is an area of high unmet need. These patients have a notoriously poor prognosis compared with BRAF wild type patients.

The BEACON trial is the first time we have seen such a positive outcome for patients with a targeted regime and for those that have exhausted their chemotherapy options.

The argument that the SOC arm in the trial (FOLFIRI plus Cetuximab) is not representative in the UK is not a valid reason to reject the regime from reimbursement. This was a global study and hence a regime available around the world needed to be used. Drugs such as Lonsurf would elicit almost no benefit to this population. Hence to deprive this group of patients access to the regime on this basis would be a travesty.

I have extensive experience with the regime and have been using it on numerous patients via the early access scheme. I can confirm first hand that the majority of

patients I have treated derived significant benefit, which has translated to living longer and with good quality of life (which would not have been possible without the drug combination)

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This drug has been life-saving for my sister and without this she would have died. My sister is [redacted] and has [redacted] children. This drug has helped to extend her life and allowed her children to have a mother. It is very sad to think that others who are in the same situation will not benefit from this despite its success. I understand the drug is expensive but can you negotiate with the drug company to get it cheaper? Also could you at least consider this drug for certain age groups or those with dependents? I beg you to reconsider withdrawing this drug solely on cost. Behind each cost is a person's life and family who will be severely impacted by a family member's death and this will also cost the NHS /government in terms of mental health costs and benefits. Kind regards, [redacted]	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Yes Are the recommendations sound and a suitable basis for guidance to the NHS? Not sure 5000 families would benefit from this. Let it pass	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
It is based upon age discrimination. It was based on a study where the average age of patients was in their 60s BUT is now being used to deny younger patients their chance of life. Encorafenib in combination with Cetuximab gives massively improved quality of life to patients where the alternative is life long chemotherapy. A separate study has shown that 75.9% of patients received some benefits to these drugs as compared with 31.2% with the usual drugs	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
After a positive outcome of the trials, why isn't this treatment being offered on the NHS? It is terrible that after all of the effort and money that goes into research for it to come down to money! Surely the aim should be to allow patients to get better, not restrict it from use. Please make this treatment available on the NHS.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No Has all of the relevant evidence been taken into account? I would like to hope so	

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I hate to think about cost when it comes to prolonging someone's life.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I hate to think about cost when it comes to prolonging someone's life

Are the recommendations sound and a suitable basis for guidance to the NHS?

I have nothing to compare this with or know how it works

Recommendations

This seems unfair for those that are in the application process, can they not get the funding still?

Committee discussion

Extending someone's life is priceless to them and their families, it is sad it comes with a price and a burden on the NHS

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

To withhold life-extending medication from young people is discriminatory and wrong. Young people in their twenties and thirties are frequently dismissed as unlikely to be suffering from cancer, despite presenting with diagnosable symptoms so that by the time the cancer has been detected, it has mestastised and the outlook is poor. The possibility of young sufferers being given a significant extension of life should not be denied. Young people deserve better. Equally, during the time people are progressing, new treatments will be perfected and made available. The CRISPR research is advancing rapidly towards an effective resolution to this particular colorectal cancer variation.

Has all of the relevant evidence been taken into account?

The evidence has been looked at.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

It appears that, in terms of clinical evidence, some willingness to confound the veracity of the trials and results is indicated, in order to support the refusal of the treatment in question on the basis of cost.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are rigid. The guidance should indicate use of the 2 chemical combination in certain circumstances where indications for progression are good.

Recommendations

It appears to me that the clinical trials results are robust and indicate that there is significant benefit to patients who, for lack of alternatives, have been backed into a corner with no escape route. The Beacon Trials have delivered positive treatment results

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes, age discrimination - the decision potentially denies life-saving drugs to younger people based upon a trial with an older average age

Are the recommendations sound and a suitable basis for guidance to the NHS?

No - the decision potentially denies life-saving drugs to younger people based upon a trial with an older average age (over 60)

I am asking you to reconsider the decision to refuse Encorafenib plus cetuximab for treating BRAF V600E mutation-positive metastatic colorectal cancer in adults where previous treatments have failed. Because this decision is based on a study where the recipients were in their 60, I believe that this is age discrimination as it potentially denies life-saving drugs to younger people based upon a trial with an older average age.
There is a need for treatments for BRAF V600E mutation-positive metastatic colorectal cancer. The current treatments are not adequate and offer little hope of life. Encorafenib plus cetuximab offers adults suffering BRAF V600E mutation-positive metastatic colorectal cancer a chance of life. (NB: a well known presenter

has stated that they have seen 100 tumours go into remission on this drug; anecdotally, others have experienced the same.)

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This drug combination is proven to be effective This drug combination is available in Europe and the US If it is not made available in the UK this discriminates against UK citizens.	

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

Evidence Review Group (ERG) critique of company response to Appraisal Consultation Document (ACD)
Warwick Evidence, 5 October 2020

This report presents the ERG's critique of the company's response to the ACD. The document follows the structure of the ACD, highlights points of relevance to the company's response and provides the ERG's comments of the response.

ACD Preamble: The assumptions necessary to bridge to the comparison with FOLFIRI are unreliable. Encorafenib meets NICE end of life criteria. The cost effectiveness estimates are higher than the usual NICE threshold. Collecting further data will not address the uncertainty. Technical engagement issues successfully resolved were the company revision to progression free survival (PFS) health state utilities and the company amended costs for drugs at the start of the model cycle.

ACD Section 3.4: FOLFIRI and trifluridine-tipiracil are relevant comparators after 1 previous line of treatment. Most people have FOLFIRI as the second-line treatment following FOLFOX as the first-line therapy. Only a small proportion have trifluridine-tipiracil as the second-line treatment following FOLFOXIRI as the first-line therapy due to higher toxicity of FOLFOXIRI.

ACD Section 3.5: Irinotecan is not a relevant comparator after 1 previous line of treatment.

ACD Section 3.6: Trifluridine-tipiracil and best supportive care (BSC) are relevant comparators after 2 previous lines of treatment.
Company Response: (see Company Response Addendum [CRA] Section 2.4): The company considered trifluridine-tipiracil to be the main comparator for encorafenib dual therapy after two previous lines of treatment (typically FOLFOX and FOLFIRI). For the small proportion of patients who received FOLFOXIRI and trifluridine-tipiracil as the first two lines of treatment, the company suggested that few patients would remain fit enough to receive encorafenib dual therapy as the third-line treatment. As a result, while any surviving patients who have gone through this treatment pathway would receive BSC at this stage, comparison with encorafenib dual therapy in this position in the treatment pathway is not appropriate.
In response to the Committee's request, the company conducted a naïve comparison using data from encorafenib dual therapy arm of the BEACON trial and from the BSC arm of Kim 2018 trial selected

from three possible options. Adjustment to the curve of overall survival (OS) for the BSC arm was made through applying a hazard ratio (HR) for BRAF mutant vs wild type patients in a similar manner as in the naïve comparison between encorafenib dual therapy and trifluridine-tipiracil.

[redacted]

[redacted]

ERG Comment: The ERG shares similar understanding with the company with regard to appropriateness of BSC as a comparator in the third-line setting based on the advice from its clinical expert. This view was corroborated by the comments made by the Royal College of Physician/National Cancer Research Institute. Given the paucity of evidence, the ERG considers the company's choice of source for BSC data (Kim et al. 2018) reasonable.

The company chose the log-logistic to keep the parametric curves chosen consistent with the parametric model chosen for comparisons with FOLFIRI and trifluridine-tipiracil.

The ERG replicated the analysis by digitising Figure 2a of Kim 2018 and estimating the Kaplan-Meier IPD using the 'ipdfc' command in Stata. The ERG then reproduced the Kaplan-Meier plot to serve as a comparison and calculated unstratified hazard ratios which were close to the HRs published in Kim 2018. The ERG fit the same parametric models to the estimated individual patient data and the model fit is presented in Table 1 below. The encorafenib plus cetuximab AIC and BIC are unchanged. In the ERG's analyses, the log-logistic curve is consistently the worst fit, with the Gompertz model having the lowest mean AIC and mean BIC between the encorafenib+cetuximab and BSC fit. Despite this, the ERG is aware that the company's approach to retaining the same functional form for both

arms being modelled was consistent with NICE Decision Support Unit's recommendation. It is also likely that the HR applied to the derived curve will be a more influential driver for cost-effectiveness as illustrated in comparison with FOLFIRI described later in this document.

Table 1: ERG's curve fitting for the BSC OS curve from Kim et al. 2018.

Model	AIC			BIC		
	Encorafenib/ cetuximab	BSC	Mean	Encorafenib/ cetuximab	BSC	Mean
Exponential	1020.28	794.5669	907.42345	1023.59	797.419	910.5045
Generalised gamma	1014.23	796.0273	905.12865	1024.15	794.8792	909.5146
Gompertz	1012.05	795.3879	903.71895	1018.67	796.2398	907.4549
Log-logistic	1012.12	805.7735	908.94675	1018.74	806.6256	912.6828
Log-normal	1014.91	799.8084	907.3592	1021.53	800.6604	911.0952
Weibull	1015.98	795.1956	905.5878	1022.6	796.0476	909.3238

The HR for BRAF mutant vs wild type used for adjusting the BSC OS curve was obtained from the same trial and this was an advantage, although the ERG notes that the HR 3.03 (95% CI 1.52 to 5.88 for OS; assumed to be the same for PFS) has very wide confidence interval (based on data from 142 BRAF wild type and 11 BRAF mutant patients) and the point estimate is higher than the estimates from Safaee Ardekani 2012 systematic review (HR 2.24, 95% CI 1.82 to 2.83 for OS) and the MRC FOCUS (HR 1.82, 95% CI 1.36 to 2.43 for OS and HR 1.14, 95% CI 0.86 to 1.52 for PFS) used in the updated analyses for the comparison with trifluridine-tipiracil. The company did not provide scenario analyses using these alternative HRs for the comparison with BSC. The ERG will provide these.

ACD Section 3.8: Using cetuximab in the control arm of BEACON does not reflect clinical practice.
Company Response: The company recognised this and conducted an indirect treatment comparison (ITC) in order to estimate and adjust for the effect of cetuximab in the BEACON control arm.
ERG Comment: The ERG considers the company's ITC potentially unreliable as it did not include all relevant evidence into consideration (see 3.11 below). The ERG is aware of the very limited and somewhat conflicting evidence with regard to the effect of adding epidermal growth factor receptors inhibitor (anti-EGFR) to cytotoxic chemotherapy as the second-line treatment for patients with BRAF V660E mutant metastatic colorectal cancer (mCRC) and the general clinical opinion that their effect is likely to be small and of limited duration. Taken in the round, the ERG suggests that comparison between the two arms of the BEACON trial provides a reasonable proxy of the relative effectiveness between encorafenib dual therapy and FOLFIRI (see 3.11 below).

ACD Section 3.9: Using irinotecan in the control arm of BEACON does not reflect clinical practice. Around 40% of BEACON control was irinotecan. It cannot be assumed that irinotecan+cetuximab is equivalent to FOLFIRI+cetuximab.

Company Response: The company maintained that the equivalence assumption is valid and carried out further statistical tests to support this (see 3.13 below).

ERG Comment: The ERG considers the company's comparison of overall survival (OS) between irinotecan+cetuximab and FOLFIRI+cetuximab using stratified Cox regression reasonably comprehensive, but the result still have a wide confidence interval and a clinically important difference cannot be ruled out (see 3.13 below). The ERG further notices that evidence from previous trials suggests anti-EGFR might have differential effects when used in combination with irinotecan or FOLFIRI, and these should be taken into account if ITC is to be used to make adjustment to derive estimations of relative effectiveness between encorafenib dual therapy and FOLFIRI based on data from the BEACON trial (see 3.11 below).

ACD Section 3.10: BEACON subsequent treatments did not reflect NHS clinical practice, which made generalising OS results to the NHS uncertain.

Company Response: The company presents the subsequent treatments used during BEACON and notes a general similarity between the arms. No clinical adjustment is made but a scenario analysis that costs the treatments if used by at least 5% of BEACON patients is presented.

ERG Comment: With regards the costing scenario the ERG thinks that this is not what was suggested under in the ACD. Given this and time constraints the ERG does not consider the costing scenario any further.

ACD Section 3.11: Analyses should seek to adjust BEACON data for cetuximab being used in the control arm, irinotecan use in the control arm and subsequent treatments not reflecting NHS practice.

Company Response: The company attempted to adjust for the effect of cetuximab using an ITC (see ERG comment below), and maintained that the equivalence assumption between irinotecan and FOLFIRI is valid (see 3.13 below). The company presented data for subsequent treatments received by BEACON trial patients and considered it unnecessary to make adjustment to BEACON data.

ERG Comment: As previously described in the ERG report, the ERG considered the company's ITC based primarily on data from Peeters 2015 potentially unreliable. While a potential effect of panitumumab (and by extension, cetuximab based on the equivalence assumption) was observed in Peeters 2015 when the anti-EGFR was used in combination with FOLFIRI, there is another trial (PICCOLO, Seymour et al. 2013, not included in the company's ITC) showing a potentially harmful effect of panitumumab (and by the same assumption, cetuximab) when the anti-EGFR was used in combination with irinotecan. Given that 42% of patients in the BEACON control arm received irinotecan+cetuximab, the evidence from PICCOLO should not be ignored if ITC was to be used to

adjust for the potential effect of cetuximab. Consequently, even if cetuximab may have some effect resulting in over-estimation of the effect of FOLFIRI based on data from the BEACON control arm, it might also have some effect resulting in under-estimation of the effect of FOLFIRI due to the 42% of patients receiving irinotecan + cetuximab. It is possible to estimate the mixed effect of cetuximab in the BEACON control arm by combining relevant estimates from Peeters 2015 and PICCOLO trials using the proportion of patients receiving FOLFIRI (58%) and irinotecan (42%) respectively in the BEACON trial as the weight:

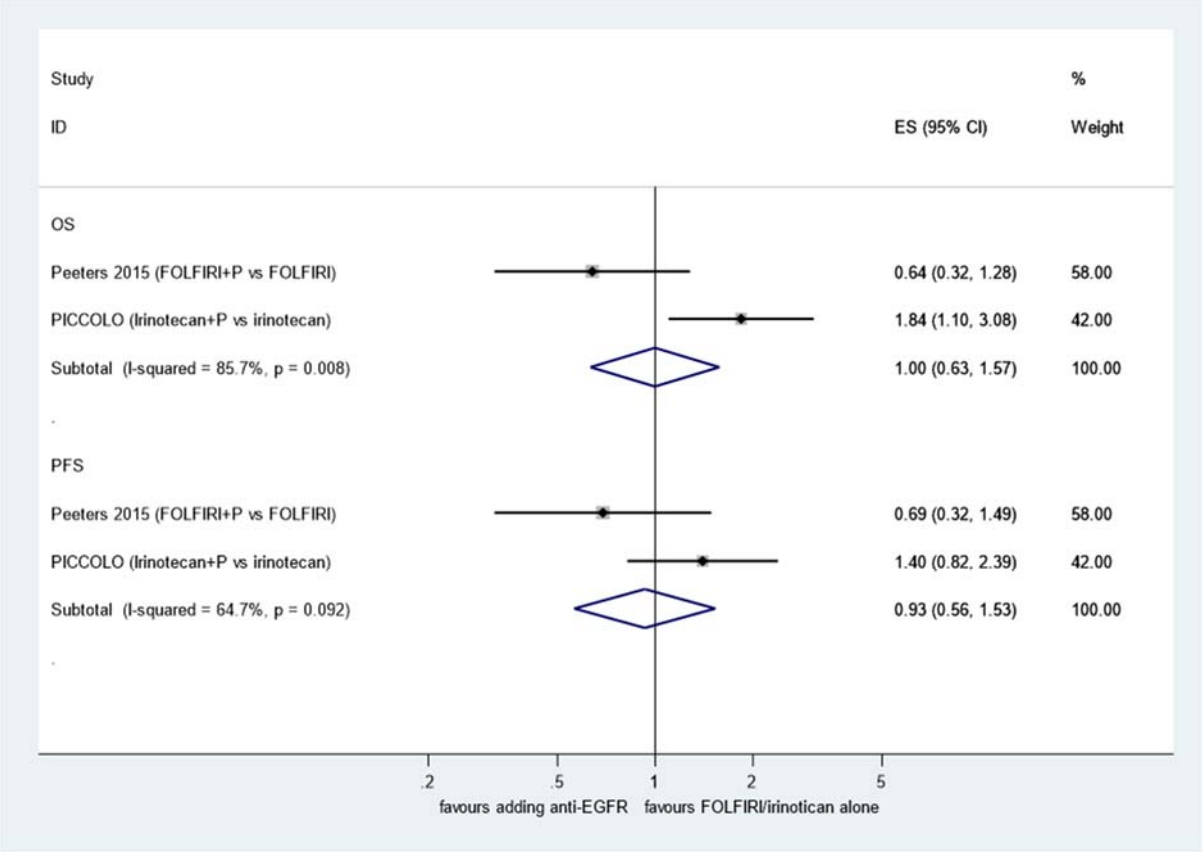


Figure 2: Estimated effect of cetuximab on BEACON control arm based on RCT data of adding panitumumab to irinotecan-based therapies in second-line setting

The results show that, based on available evidence, the effects of cetuximab among the FOLFIRI and irinotecan subgroups might largely cancel each other out in the BEACON control arm, and therefore the data from the BEACON control arm remain a reasonable estimate for FOLFIRI/irinotecan even in the presence of cetuximab. If equivalence between FOLFIRI and irinotecan was not assumed, further adjustment assuming better effectiveness of FOLFIRI relative to irinotecan would suggest that the effect of FOLFIRI was under-estimate based on the BEACON control arm. The ERG therefore maintains that company's ITC is highly uncertain, and data from randomised comparison between

encorafenib dual therapy and the control arm in the BEACON trial may offer a reasonable proxy of relative treatment effect in the absence of more reliable data.

The ERG notes that in the response to ACD submitted by the Royal College of Physician and the National Cancer Research Institute, a pooled analysis from CRYSTAL and OPUS trials in the first-line treatment setting for metastatic colorectal cancer (mCRC) was cited (Boyemeyer 2012). Based on this analysis, the addition of cetuximab to FOLFIRI or FOLFOX-4 extended the median survival by approximately four months compared with FOLFIRI/FOLFOX-4 alone among patients with BRAF V600E mutation. The corresponding HRs (for FOLFIRI/FOLFOX-4 + cetuximab vs FOLFIRI/FOLFOX-4 were OS 0.62 (0.36 to 1.06) and PFS 0.67 (0.34 to 1.29), which appear similar to HRs reported by Peeters 2015. However, the ERG is aware that two subsequent meta-analyses which included data from CRYSTAL and OPUS as well as other trials of anti-EGFRs in first-line and/or second-line setting showed heterogeneous findings and the pooled HRs suggested smaller or no effect for adding anti-EGFR to chemotherapy: Rowland et al. 2015: second-line setting, OS 1.06, 95% CI 0.48 to 2.36, I^2=67% and PFS 0.84, 95% CI 0.46 to 1.51, I^2=42%; Pietrantonio et al. 2015, various lines, OS 0.91, 95% CI 0.62 to 1.34 and PFS 0.88; 95% CI 0.67 to 1.14.

ACD Section 3.12: Cetuximab and panitumumab should be considered equivalent.

ACD Section 3.13: Equivalence between FOLFIRI and irinotecan is unproven. BEACON control arm differences could be due to confounding due to a lack of randomisation. Further analyses including a log-rank test and analyses adjusted for potential confounders should be presented.

Company Response (CRA Section 1, pages 1-2): The company stated that the BEACON trial was designed on the basis of equivalence between irinotecan+cetuximab and FOLFIRI+cetuximab, and was not sufficiently powered to detect differences between encorafenib dual therapy with either subgroups within the BEACON control arm. The company reported a log rank test for overall survival (OS) stratified on ECOG performance status, source of cetuximab, and prior irinotecan use at randomisation based on May 2020 data cut and obtained a hazard ratio (HR) of 1.11 (95% CI [redacted] to [redacted], one sided p=[redacted]) for irinotecan+cetuximab vs FOLFIRI+cetuximab. In response to the Committee's request, the company conducted a further stratified multivariate Cox regression in order to adjust for potential confounders, and obtained a HR [redacted], 95% CI [redacted] to [redacted], 2-sided p=[redacted]). The company stated that these analyses further support the equivalence between irinotecan+cetuximab and FOLFIRI+cetuximab.

ERG Comment: the additional adjustments made in the stratified multivariate Cox regression, which covered age, sex, removal of primary tumour, baseline CRP, side of tumour, number of organs involved, presence of liver metastases, number of prior regimens for metastatic disease and prior use of oxaliplatin appear to be comprehensive, although residual confounding remains possible. The analysis was under-powered and therefore an important difference cannot be ruled out. The company

did not report comparison of PFS curves between the two subgroups. The ERG carried out a log-rank test using data (August 2019 data cut) previously supplied by the company in response to ERG's clarification question and obtained a p-value of [redacted]. The ERG does not have the data for adjustment of potential confounders.

ACD Section 3.14: The company's ITC is highly uncertain. Without an appropriate ITC, analysis based upon BEACON head to head results is preferred. But both approaches are uncertain, and both will be taken into account.

Company Response: The company preferred base case appears to be the ITC, but a full set of results applying the trial head to head results in also presented.

ERG comment: This suggests that the base case should not apply the ITC results for the effect of adding cetuximab to FOLFIRI for the BRAF V600E mutant population, but that scenario analyses should be presented that do. This may conflict with ACD section 3.34. The ERG also recalls the AC discussing the duration of any cetuximab effect. In the light of this the ERG will present a full set of analyses that do not apply the company ITC estimate for the effectiveness of cetuximab and a full set of analyses that do apply the company ITC estimate for the effectiveness of cetuximab, coupled with scenario analyses that vary the duration of the ITC estimate for the effectiveness of cetuximab[1].

ACD Section 3.15: It is appropriate to take RECOURSE into account as part of the evidence base.

Company Response: The company in effect updates its analysis that applies the BRAF V600E HR of 4.00 the RECOURSE trial data, also presenting analyses for the other HRs that have been previously explored.

ERG Response: The ERG still has concerns about the degree to which the application of the HR shifts the RECOURSE trial (Mayer et al. 2015) data from being similar to that of the BEACON control arm to suggesting a very poor OS for those receiving trifluridine-tipiracil. Time constraints limit the ERG to presenting the April 2019 data cut in the figure below, but the overall picture in terms of the similarity between RECOURSE and the BEACON control arm will still broadly hold.

[1] Implemented by assuming $S_F(t)=S_{F+C}(t)^{HR}$ up to the maximum duration of the cetuximab HR, then calculating $S_F(t_i)= S_F(t_{i-1})*(S_{F+C}(t_i)/S_{F+C}(t_{i-1}))$. Note that this requires the HR implied for FOLFIRI+cetuximab vs FOLFIRI and the FOLFIRI+cetuximab curve to be applied, rather than the HR for encorafenib+cetuximab vs FOLFIRI and the encorafenib+cetuximab curve being applied.

3

The ERG will present scenario analyses over the range of the HRs previously explored, including unity.

ACD Section 3.16: The hazard ratios for BRAF V600E mutant versus wild type vary wildly within the Safee et al meta-analysis. Which is most appropriate is uncertain. The naïve comparison is uncertain.

Company Response (CRA Section 2.3, pages 16-21): The company acknowledged the wide range of HRs reported in the literature, and suggested that the estimated HR from Safaee et al 2012 could be considered as the most robust as it was derived from a systematic review of multiple studies. The company provided cost-effectiveness analyses using three different HR estimates discussed in the Committee meeting.

ERG Comment: The ERG also acknowledges the substantial variation in the HRs reported in the literature, and notes that the Safaee meta-analysis included studies of heterogeneous mCRC patients (e.g. both metastatic and earlier stages) from around the world. The pooled estimate was associated with a high level of statistical heterogeneity (I^2 >70%) between the included studies. Consequently, the estimate from the UK-based MRC FOCUS trial (Richman 2009) that the ERG proposed during technical engagement remains one of the most plausible estimates. The ERG cautions that the patient populations based on which the HRs were derived (i.e. often in earlier stages of disease/places in the treatment pathway) were very different from the patient population to which the HR is applied (i.e.

patients from the trifluridine-tipiracil arm of RECOURSE, most of whom had 3 or more prior therapies). Consequently, the results of the naïve comparison and any cost-effectiveness analyses based on this would be highly uncertain irrespective of which HR is used to 'adjust for' the survival curve from the RECOURSE trial. The ERG further notes that in the adjustment for both the trifluridine-tipiracil arm of the RECOURSE and the BSC arm of Kim 2018, the HRs for BRAF V600E mutant vs wild type were applied to survival curves of the whole trial arms which might have included both BRAF V600E mutant and wild type patients (rather than exclusively BRAF wild type patients). This means the baseline population's survival, from which the adjustment was made, might be too low, and this effect would be carried forward into the adjusted curves.

ACD Section 3.17: The company model is appropriate for decision making.

ACD Section 3.18: The May 2020 data cut should be taken into consideration for decision making.
Company Response: The company updates the curves within the model and the quality of life values to reflect the May 2020 data cut.
ERG Comment: The ITC has not been updated for the May 2020 BEACON trial OS HR. The ERG has calculated the unadjusted BEACON trial OS HR for DCO1 and DCO2: 0.5997 (0.4743, 0.7584) and 0.6071 (0.4899, 0.7524) respectively. While the ITC relies upon OS HRs adjusted for covariates, the unadjusted HRs suggest that updating the ITC for the May 2020 data cut is likely to have little effect upon results.

ACD Section 3.19: OS should be modelled using the piecewise approach.
Company Response: The company applied a piecewise approach for OS modelling, with the KM data for the first three months and smooth parameterised curves thereafter.
ERG Comment: The company has not provided the parameter estimates and the curves in the model are implemented as pure number rather than as a function of the parameter estimates. As a consequence, the ERG cannot state that the company has implemented the piecewise curves correctly. Visual inspection suggests that the company has adopted the same approach as the ERG.

ACD Section 3.20: The May 2020 data cut should be explored with a fuller presentation of piecewise curves.
Company Response: The company presents the usual set of curves together with their AIC and BIC.
ERG Comment: As noted above, the curves are presented as pure number. The ERG has not had time to cross check that the curves fit the supplied May 2020 KM data.
The company tabulates the OS by functional form for encorafenib+cetuximab in Table 4 (p.7) of its ACD response addendum,and presents the curves in Figure 1 of the addendum. The ERG finds Figure 1 quite difficult to interpret due to it covering the 10 year time horizon of the economic modelling.

The ERG also thinks that more attention needs to be given to the numbers at risk in the construction of the encorafenib+cetuximab Kaplan Meier curve. As the company Table 4 footnote suggests: "*2.5 year estimate is subject to some uncertainty due to low numbers of patients at risk*".

As can be seen from the above, even at the 2 year point the numbers at risk are somewhat below the S(t) curve. At two years S(t)= but this is based upon of the initial 220 patients remaining at risk. At 2.5 years S(t)= but this is based upon of the initial 220 patients remaining at risk. As a consequence, there is relatively little statistical weight in the two long steps to the right of the KM S(t) curve. The eye is naturally drawn to these when assessing the goodness of fit of the parameterised curves, but this may place too much importance to them.

4

In the light of the numbers at risk towards the tail of the KM S(t) curve, it is difficult to particularly distinguish between the parametrised curves by visual inspection. It can be argued that the log-logistic, generalised gamma and Weibull all remain plausible candidates.

The ERG augments Table 4 of the company ACD response addendum with the proportions modelled as surviving for the other parameterised fits.

Table 2: Encorafenib KM and parameterised curves OS May 2020

Month	12	18	24	30	36	48	60	120
GOMP LOGN LOGL GAMM WEIB EXPO								
KM S(t) N at risk								

The 10 year survival proportions are non-negligible for many of the curves. This calls into question either the reasonableness of using the curves to extrapolate to 10 years or the 10 year time horizon. For instance, for the company preferred log-logistic the proportion remaining alive at 10 years in the encorafenib arm is modelled as [redacted].

The ERG replicates Figure 1 if the company ACD response addendum for completeness and ease of reference.

[redacted]

[redacted]

ACD Section 3.21: Experts suggest that survival with FOLFIRI is less than 10% at 3 years and 5% at 5 year. The ERG exponential curve is too pessimistic.

Company Response: The company presents the proportions modelled as surviving at various points for encorafenib, BEACON control and FOLFIRI, with the FOLFIRI estimates assuming that the ITC results for the effect of cetuximab should be applied indefinitely.

ERG Comment: There is an interaction between the assumed duration of the cetuximab effect when added to FOLFIRI and the choice of curve.

The company approach of applying the BEACON encorafenib log-logistic OS curve and deriving the FOLFIRI OS curve by applying the ITC OS HR of 2.56 should be broadly equivalent to deriving the FOLFIRI OS curve by applying the inverse of the panitumumab[2] HR, 1.56, to the BEACON control

[2] Taken from ERG report Table 8 values from Peeters et al for FOLFIRI vs FOLFIRI+panitumumab, and assuming equivalence of panitumumab with cetuximab.

arm log-logistic OS curve. These two approaches show a good correspondence, suggesting ICERs of £87,330 per QALY and £87,535 per QALY respectively[3].

The approach of applying OS and PFS HRs to remove the effect of cetuximab use from the BEACON control arm curves means that the duration of the cetuximab effect can be explored.

Note that in common with all the company PF F2 analyses, all the reported ICERs are based upon the company log-logistic TTD curve due to this being the only curve that the company has provided. In the absence other data, the FOLFIRI TTD curve has been estimated by applying the PFS HR to the BEACON control arm TTD curve in the same manner it is applied to the BEACON control arm PFS curve to estimate the FOLFIRI PFS curve.

Table 3: FOLFIRI modelled 3 year OS percentage

	Duration of cetuximab effect when added to FOLFIRI					
OS form	Life	2 year	1 year	6 month	3 month	None
Gompertz						
Log-normal						
Log-logistic						
Gen. gamma						
Weibull						
Exponential						

Table 4: FOLFIRI modelled 5 year OS percentage

	Duration of cetuximab effect when added to FOLFIRI					
OS form	Life	2 year	1 year	6 month	3 month	None
Gompertz						
Log-normal						
Log-logistic						
Gen. gamma						
Weibull						
Exponential						

The above shows that regardless of which OS functional form is assumed for the BEACON control arm, conditioning it by the relevant ITC input cetuximab HR for the lifetime of the model to derive the FOLFIRI OS curve results in FOLFIRI OS percentages at 3 years and at 5 years that are

[3] Both retain costing based upon PFS curves for comparability, and similarly estimate the FOLFIRI PFS curve by applying the relevant PFS HR to the relevant BEACON PFS curve.

somewhat below the 10% and 5% maxima of the ACD. This may be an argument for restricting the duration of the assumed cetuximab effect when added to FOLFIRI among BRAFV600 patients.

Table 5: Undiscounted OS months by curve and duration of cetuximab effect with FOLFIRI

	Duration of cetuximab effect when added to FOLFIRI					
OS form	Life	2 year	1 year	6 month	3 month	None
Gompertz	[redacted]					
Log-normal						
Log-logistic						
Gen. gamma						
Weibull						
Exponential						

The net gain in months survival can also be presented, alongside the percentage of this gain that is modelled as occurring after progression when treatment with encorafenib has or will soon be stopped.

Table 6: Undiscounted OS gain in months by curve and duration of cetuximab effect with FOLFIRI

	Duration of cetuximab effect when added to FOLFIRI					
OS form	Life	2 year	1 year	6 month	3 month	None
Gompertz	[redacted]					
Log-normal						
Log-logistic						
Gen. gamma						
Weibull						
Exponential						

The curves with the longest tails model the longest OS for encorafenib and, by implication, FOLFIRI, but the effect is larger for encorafenib resulting in a larger net OS gain. If the effect of cetuximab is long lived, removing it from FOLFIRI+cetuximab considerably lessens the resulting FOLFIRI OS and so increases the net gain from encorafenib over FOLFIRI. It also results in somewhat more of the overall net OS gain being modelled as occurring after progression and when treatment with encorafenib has or will soon be stopped:

[redacted].

ACD Section 3.22 Using PFS KM data rather than fitting a curve is reasonable. Results were not particularly sensitive to this. PFS KM data should be used.

Company Response: The company applies the KM PFS curves. To derive the PFS KM curve for FOLFIRI in its ITC based analyses that company applies the ITC PFS HR of 3.33 to the BEACON encorafenib PFS curve.

ERG Comment: None.

ACD Section 3.23: It is reasonable to assume the same treatment effect regardless of previous lines of treatment. Given the uncertainty around the BRAF V600E mutant to wild type OS hazard ratio the cost effectiveness estimates compared to trifluridine-tipiracil are very uncertain.

Company Response: The company does not analyse the BEACON data by number of previous treatments in the response to ACD. The comparison with trifluridine-tipiracil is based upon a naïve comparison with the BEACON encorafenib dual therapy arm. The company presents three sets of analyses, applying the HRs of Peeters et al 2015, Safee et al2012 and MRC FOCUS (Richman et al 2009) as described in earlier in 3.16.

ERG Comment: The forest plot presented in Appendix E (p.115) of the original company submission shows that the HRs for OS for encorafenib dual therapy vs control were [redacted] between the subgroups of patients who had one versus two prior therapies. By contrast, there is absence of evidence for the effectiveness of trifluridine-tipiracil for BRAF V600E mutant population. The ERG considers HRs from the UK-based MRC FOCUS trial to be potentially more plausible estimates but emphasises the high level of uncertainty related to the naïve comparison as describe above in 3.16.

ACD Section 3.24: Adjusting for subsequent treatments is reasonable.

Company Response (CRA Section 2.2.2.1, p.12-15): The company suggested that most subsequent treatments were standard therapies and were similar between treatment arms. Only a small number of patients received immunotherapies ([redacted] [redacted%] patients in the encorafenib arm and [redacted] [redacted%] patients in the control arm) and these were very unlikely to have an impact on survival estimates generated within the trial. No adjustment on survival evidence was made, but scenario analyses incorporating the costs of subsequent treatments were provided.

ERG Comment: the company provided a detailed list of subsequent anti-cancer therapy in Table 10 of its ACD response addendum (p. 13). Notable differences between encorafenib dual therapy and control arms included 'irinotecan combination + VEGFi' [redacted]% vs [redacted]%, 'irinotecan combination' [redacted]% vs [redacted]%, and 'BRAFi + MEKi + EGFRi' [redacted]% vs [redacted]%. Interpretation of the data is difficult due to the large number of different regimens (combinations of drugs) listed. The sum of patients receiving individual regimens seems to exceed the total number of patients receiving 'any regimen'

listed at the top of the table. Overall the ERG considers major bias in favour of encorafenib in estimated relative survival gain due to subsequent treatments unlikely.

ACD Section 3.25: Waning of effect does not need to be considered.
Company Response: None.
ERG comment: The ERG assumes this relates to the clinical effectiveness reported for BEACON. In the light of comments, the ERG explores varying the duration of effect for the addition of cetuximab to FOLFIRI among BRAF V600E mutant patients.

ACD Section 3.26: The utility estimates restricted to FOLFIRI+cetuximab patients are appropriate.
Company Response: The company has revised the quality of life estimates to apply the May 2020 data cut values, along the lines suggested in the ACD.
ERG comment: None

ACD Section 3.27: Time to treatment discontinuation (TTD) should be used for costing. But this is uncertain and scenarios should be explored.
Company Response: TTD costing cannot be applied for scenarios based upon applying hazard ratios because no TTD curve is available for the comparator. It can only be applied for the direct head-to-head comparison of the BEACON encorafenib arm with the BEACON control arm. The company presents parameterised log-logistic TTD curves for this analysis.
ERG Comment: As per the original ERG report it is possible to present scenario analyses which apply the TTD curve for encorafenib and make assumptions about the comparator arm TTD curve. Because the company base case analysis applies the ITC PFS HR to the BEACON encorafenib arm PFS curve to derive the FOLFIRI PFS curve, the ERG thinks that the most reasonable approach is to apply the ITC PFS HR to the BEACON encorafenib TTD curve. Or when deriving the FOLFIRI PFS curve by applying the relevant HR to the BEACON control arm PFS curve, to apply the same HR to the BEACON control arm TTD curve. Given the cost differences between encorafenib treatment and the comparator arm treatment assuming TTD=PFS will generally bias the analysis in favour of encorafenib.

ACD Section 3.28: Mean dose intensities should be used.
Company Response: The company retains the mean encorafenib RDI of [redacted] throughout.
ERG Comment: The ERG still thinks that averaging across a patient with 1 month's exposure and an RDI of 50% and a patient with 24 month's exposure and an RDI of 100% to arrive at a mean RDI of 75% that is applied to all patients while on treatment will be biased and will probably underestimate encorafenib costs. The ERG thinks that individual patients RDIs are likely to be related to their

duration of exposure. The data is highly skewed. No evidence to the contrary has been presented. But this aspect may be moot given the requirement of ACD section 3.29.

ACD Section 3.29: 10% oral drug wastage and 0% IV drug wastage is appropriate.
Company Response: The company does not include encorafenib wastage in its base cases. It presents sensitivity analyses which retain the mean encorafenib RDI of [redacted] for 90% of patients which results in an encorafenib cost per model cycle of [redacted] and assumes an encorafenib RDI of 100% for 10% of patients which results in an encorafenib cost per model cycle of [redacted], hence an average encorafenib cost per model cycle of [redacted]: a 1% increase on the base case.
ERG Comment: The ERG will increase the encorafenib costs by 10% to account for wastage. It should be noted that in effect this still results in an RDI of less than 100%. Due to encorafenib being dispensed in packets applying a tablet based RDI may still be too optimistic, and there remains an argument for applying an RDI of 100%.

ACD Section 3.32: It is appropriate to make pairwise comparisons rather than present a fully incremental analysis.
Company Response: Pairwise comparisons are presented.
ERG Comment: None

ACD Section 3.34: The modelling should:

- Present analyses that split the control arm, adjusting for potential confounders and presenting log-rank tests for OS and PFS (3.13)
- Use the clinical efficacy data from BEACON (3.20)
- Use the ITC HR to adjust for the use of cetuximab (3.21)
- Use the May 2020 data cut (3.18)
- Use a full range of piecewise fits of OS (3.19, 3.20, 3.21)
- Adjust OS and costs for subsequent treatments not used in the NHA (3.10, 3.24)
- Use KM PFS data from BEACON (3.22)
- Use adjusted RECOURSE data (3.16)
- Apply 10% oral drug wastage and 0% IV drug wastage (3.29)
- Use TTD for costing (3.27)
- For those with more than 1 prior treatment consider BSC as a comparator (3.6)

Company Results: vs FOLFIRI

The ERG has not replicated the company scenario analysis that includes the costs of the BEACON trial subsequent treatments.

Table 7: Company analyses vs FOLFIRI

OS form	PF F1	PF F2
Gompertz	£71,922	£124k
Log-normal	£81,099	£145k
Log-logistic	£82,791	£159k
Gen. gamma	£96,502	£177k
Weibull	£115k	£201k
Exponential	£134k	£232k
Log-logistic*	£83,390	£160k
*Assuming 10% of encorafenib patients have some wastage		

Company Results: vs trifluridine-tipiracil

The ERG has not replicated the company scenario analysis that includes the costs of the BEACON trial subsequent treatments.

Table 8: Company cost effectiveness analyses vs trifluridine-tipiracil: list prices

HR Source	Peeters	Safee	FOCUS	Unity**
OS HR	4.00	2.24	1.82	1.00
PFS HR	3.57	2.24	1.14	1.00
Gompertz	£55,111	£59,789	£59,901	£72,665
Log-normal	£61,753	£67,827	£69,629	£102k
Log-logistic	£63,109	£69,221	£70,960	£106k
Gen. gamma	£71,232	£79,303	£81,395	£113k
Weibull	£81,167	£92,147	£95,722	£136k
Exponential	£82,324	£96,588	£103k	£207k
Log-logistic*	£63,585	£69,754	£71,536	£107k
* Assuming 10% of encorafenib patients have some wastage ** ERG additional scenario				

Company Results: vs BSC

It appears that there is an error in the company BSC modelling with it applying the BEACON control arm PFS Kaplan Meier data rather than the smooth HR adjusted log-logistic curve. It is not possible for the ERG to apply the BSC KM curve as this has not been supplied by the company. The ERG presents the company estimates and the estimates corrected to apply the BSC loglogistic PFS curve. The correction has minimal effect upon results.

Table 9: Company analyses vs BSC

OS form	Company	Corrected
Gompertz	£62,113	£62,042
Log-normal	£69,673	£69,535
Log-logistic	£71,164	£71,006
Gen. gamma	£80,993	£80,703
Weibull	£93,490	£93,004
Exponential	£95,597	£94,943
Log-logistic*	£71,655	£71,493
* Assuming 10% of encorafenib patients have some wastage		

ERG adjustments to company modelling

On the assumption that the ITC results should be applied to remove the effects of cetuximab, hazard ratios taken from the ITC can be applied to the encorafenib + cetuximab OS and PFS curves to derive the FOLFIRI OS and PFS curves. Alternatively, appropriate hazard ratios taken from the inputs to the ITC can be applied to the BEACON control arm OS and PFS curves to derive the FOLFIRI OS and PFS curves.

- For the encorafenib + cetuximab OS and PFS curves apply HRs of 2.56 and 3.33 respectively
- For the BEACON control arm OS and PFS curves apply HRs of 1.56 and 1.45 respectively

The approach of the second bullet is intuitively more appealing, and has the additional advantage that the duration of cetuximab effect among BRAF V600E mutant patients can be varied.

The company modelling does not:

- Correct the cell referencing error for the FOLFIRI first cycle adverse event costs and does not base these costs on the control arm of the BEACON trial. The ERG modelling corrects this and bases these costs on the control arm of the BEACON trial.
- Apply the lower FOLFIRI prices or the CMU EMIT costs and weights for fluocinolone. The ERG modelling makes these revisions.
- Apply the ERG revised PFS resource use estimates.
- Assume 10% oral wastage as discussed above. The ERG applies the BEACON mean RDIs, while increasing the encorafenib cost by 10% to account for wastage.
- Apply TTD costing, with the exception of the modelling the compares encorafenib arm with the BEACON control arm.

The effect of these changes upon the company preferred base case, PF F1 OS log-logistic, ICER of £82,791 per QALY at list prices are presented below.

Table 10: Effect of ERG model revisions: Comparison with FOLFIRI

	List price
Company PF F1: OS log-logistic	£82,791
FOLFIRI AE costings	£82,180
FOLFIRI costs	£83,009
ERG PFS resource use	£83,494
10% oral wastage	£87,012
TTD costing	£94,104
Cumulative	£99,197

The cumulative effect of these changes on the PF F2 Log-logistic OS ICER of £158,682 per QALY is to increase it to £167,609 per QALY, the effect being less marked as the company analysis for this scenario applies TTD costing.

Exploring the effect of varying the duration of the effect of cetuximab when added to FOLFIRI, by applying the Peeters et al HRs to the BEACON control arm to derive the FOLFIRI curves results in the following ICERs.

Table 11: ICER by OS curve and duration of cetuximab effect with FOLFIRI

	Duration of cetuximab effect when added to FOLFIRI					
OS form	Life	2 year	1 year	6 month	3 month	None
Gompertz	£85,548	£87,210	£91,839	£102k	£116k	£131k
Log-normal	£97,128	£99,071	£104k	£115k	£134k	£154k
Log-logistic	£99,678	£102k	£108k	£122k	£143k	£168k
Gen. gamma	£115k	£117k	£122k	£136k	£159k	£186k
Weibull	£135k	£136k	£142k	£157k	£181k	£213k
Exponential	£152k	£153k	£159k	£177k	£204k	£246k

Modelling vs trifluridine-tipiracil

The company notes that TTD curves are not available for trifluridine-tipiracil. But if costing based upon TTD curves is preferred, given the often extremely limited PFS that is modelled for trifluridine-tipiracil compared to the somewhat more extensive PFS for encorafenib+cetuximab the difference between the TTD curve and the PFS curve for trifluridine-tipiracil will be limited in any case. As a consequence, as a simple assumption the ERG increases the trifluridine-tipiracil discounted treatment

costs estimated using the PFS curve by the same proportion as the encorafenib discounted treatment costs are increased by applying the TTD curve rather than the PFS curve.

The ERG model revisions have the following effects upon the Safee based analysis.

Table 12: Effect of ERG model revisions: Comparison with trifluridine-tipiracil

	List price
Company PF T1: OS log-logistic	£63,109
ERG PFS resource use	£63,323
10% oral wastage	£66,466
TTD costing	£71,190
Cumulative	£75,204

The full set of analyses is as follows.

Table 13: ERG cost effectiveness analyses vs trifluridine-tipiracil: list prices

HR Source	Peeters	Safee	FOCUS	Unity
OS HR	4.00	2.24	1.82	1.00
PFS HR	3.57	2.24	1.14	1.00
Gompertz	£65,615	£71,310	£71,648	£87,119
Log-normal	£73,579	£80,942	£83,302	£123k
Log-logistic	£75,204	£82,608	£84,893	£127k
Gen. gamma	£84,935	£94,703	£97,463	£135,714
Weibull	£96,826	£110k	£115k	£163k
Exponential	£98,143	£115k	£124k	£248k

Modelling vs BSC

The company does not comment upon the TTD curves for the comparison with BSC. But it can be noted that a TTD curve is not required for BSC, and as a consequence there is no bar to applying the encorafenib TTD curve. The ERG applies it model revisions. The ERG augments the Kim HR analysis with the other BRAFV600 HRs that have been applied during the assessment: Peeters, Safee, MCR UK FOCUS and unity.

The ERG model revisions have the following effects upon the Kim based analysis

Table 14: Effect of ERG model revisions: Comparison with BSC

	List price
Company PF T1: OS log-logistic	£71,164
SAE cell reference	£70,664
BSC PFS curve referencing	£71,006
ERG PFS resource use	£71,768
10% oral wastage	£74,629
TTD costing	£80,347
Cumulative	£83,965

Table 15: ERG cost effectiveness analyses vs BSC: list prices

HR Source	Peeters	Kim	Safee	FOCUS	Unity
OS HR	4.00	3.03	2.24	1.82	1.00
PFS HR	3.57	3.03	2.24	1.14	1.00
Gompertz	£70,042	£73,334	£78,538	£83,786	£113k
Log-normal	£78,784	£82,211	£87,935	£94,217	£143k
Log-logistic	£80,323	£83,965	£90,035	£96,864	£160k
Gen. gamma	£90,623	£95,475	£103k	£112k	£175k
Weibull	£103k	£110k	£122k	£135k	£225k
Exponential	£105k	£112k	£125k	£139k	£272k

Conclusions

The major challenge in estimating relative effectiveness between encorafenib dual therapy and its main comparator FOLFIRI as the second-line treatment arises from the control arm of the BEACON trial, which departed from FOLFIRI in two ways; (1) 42% of the patients in the control arm received irinotecan rather than FOLFIRI based on treating physician's choice; (2) all control arm patients received cetuximab. The company assumed equivalence between irinotecan and FOLFIRI but this was challenged by the Committee. The company reported a stratified Cox regression in order to compare OS between irinotecan and FOLFIRI subgroups while adjusting for potential confounders. The result, while not statistically significant, cannot rule out important difference and the point estimate was compatible with the hazard of death being [redacted] for patients receiving irinotecan + cetuximab compared with those receiving FOLFIRI + cetuximab. ERG's log-rank test for PFS[redacted]. Consequently, further analyses based on BEACON control arm data could have under-estimate the effect of FOLFIRI + cetuximab. On the other hand, the company suggested that the BEACON control arm data would have over-estimated the effects of FOLFIRI due to the concomitant use of cetuximab. The ITC conducted by the

company essentially tried to 'adjust away' the effect of cetuximab by apply HRs obtained from Peeters 2015 trial, which suggested a rather large effect of cetuximab that also becomes a key driver for estimated cost-effectiveness. The ERG highlighted potential issues of relying on HRs from the single trial, and pointed to other available evidence which the Committee may wish to consider.
The absence of documented evidence for the effectiveness trifluridine-tipiracil for mCRC patients with BRAF V600E continues to be the key issue for this comparator. The validity and accuracy of using BRAF V600E mutant vs wild type HR to make adjustment from the intervention arm of the RECOURSE trial remain highly uncertain as the ERG described. The comparison with BSC shares similar methodological challenges, but also has issues concerning clinical relevance as the company and other stakeholders pointed out.

The company provides the May 2020 OS KM data and the encorafenib piecewise fits to this. The encorafenib OS KM data has a long tail to the right, but there are very few patients at risk and little weight should be placed on this portion of the KM plot. Visual inspection of the curves' fit to the OS KM data may suggest that the log-logistic, generalised gamma and Weibull remain plausible candidates. Extrapolating some of these curves to 10 years suggests non-trivial proportions remaining alive, e.g. [redacted] for the company preferred log-logistic. This suggests that either the time horizon is too short or some curves' extrapolations are too optimistic.
To compare encorafenib with FOLFIRI the company explores two methods: fitting curves to the BEACON encorafenib arm and applying the company ITC HRs to the encorafenib curves to derive the FOLFIRI curves; and, a direct head-to-head comparison of the BEACON encorafenib arm with the BEACON control arm. The ERG thinks that a third method provides additional useful information: estimating the FOLFIRI curves by applying the relevant HRs to remove any effect of cetuximab from the BEACON control arm curves. Applying the HRs for the time horizon of the model corresponds with the first company method, while applying them for t=0 corresponds to the second company method. Interim durations can then be explored. If the HRs are applied for the time horizon very few FOLFIRI patients are modelled surviving to 3 years, well below the 10% maximum of the ACD.
The OS curves with longer tails suggest larger net OS gains from encorafenib over FOLFIRI, and that only a minority of the net OS gain is realised due to extending PFS with the majority of the OS gain being due to extending PPS.
The company does not apply the ACD 10% oral wastage, but rather assumes that 10% of patients will incur wastage so increasing the encorafenib costs by 1%. The ERG applies 10% wastage to the encorafenib direct drug costs, while retaining the BEACON mean RDI.
The company only applies TTD costing for the head-to-head comparison with the BEACON control arm, and otherwise applies PFS costing. This seems likely to bias the analysis given relative drug costs. There is no reason not to apply TTD costing for the comparison with BSC because BSC does

not require a TTD curve. Where required, the ERG infers TTD curves for the comparator arm by either applying the PFS HR to the encorafenib TTD curve or assuming that it is higher than the PFS curve by the same proportion that the encorafenib TTD curve is above the encorafenib PFS curve.
The naïve comparison with trifluridine-tipiracil using the RECOURSE data remains very uncertain and the ERG again draws attention to the similarity of the RECOURSE OS curve and the BEACON control arm OS curve. Both the company and the ERG provide a range of scenarios that vary the BRAF V600E mutant vs wild type HRs that are applied to the RECOURSE data.
The naïve comparison with BSC using the Kim trial data is similarly uncertain. The ERG provides a range of scenarios that vary the BRAF HRs that are applied, mirroring its analyses for the comparison with trifluridine-tipiracil.
Due to the very limited time available to the ERG to respond to the company ACD comments all ERG analyses have been produced at speed. The ERG asks that all OS presentations and ICERs of this report are sent to the company prior to AC2. The ERG has also produced a stand-alone worksheet that outlines the ERG derivation of the various curves and asks that this be sent to the company prior to AC2.

References

Bokemeyer C, Cutsem EV, Rougier P, Ciardiello F, Heeger S, Schlichting M, et al. 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. 2012;48(10):1466-75.

Kim TW, Elme A, Park JO, Udrea AA, Kim SY, Ahn JB, et al. Final Analysis of Outcomes and RAS/BRAF Status in a Randomized Phase 3 Study of Panitumumab and Best Supportive Care in Chemorefractory Wild Type KRAS Metastatic Colorectal Cancer. Clin Colorectal Cancer. 2018;17(3):206-14.

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. New England Journal of Medicine. 2015;372(20):1909-19.

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.

Pietrantonio F, Petrelli F, Coinu A, Di Bartolomeo M, Borgonovo K, Maggi C, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: A meta-analysis. European Journal of Cancer. 2015;51(5):587-94.

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.

Seymour MT, Brown SR, Middleton G, Maughan T, Richman S, Gwyther S, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. The lancet oncology. 2013;14(8):749-59.

Richman SD, Seymour MT, Chambers P, Elliott F, Daly CL, Meade AM, et al. 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. J Clin Oncol. 2009;27(35):5931-7.

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

Evidence Review Group (ERG) critique of company response to Appraisal Consultation Document (ACD)

Produced by: Warwick Evidence

Date completed: 9 October 2020

We can confirm that we have been able to reproduce the OS curves fitted to the latest data cut of BEACON. Our curves showed satisfactory agreement with those implemented by the company. We are now satisfied with the company's implementation of the piecewise models for OS, which begin extrapolation from 3 months in the economic model.

We have also been able to recreate the IPD for TTD from BEACON, which required manipulation of the information provided by the company. We have successfully managed to fit a full set of parametric curves and verified the company's claim that the log-logistic is the model with the lowest statistical goodness of fit, which was previously unsupported with evidence. The estimates from our log-logistic model was almost identical to the company's reported curve, with only negligible inconsequential differences observed. We are satisfied that the log-logistic curve can be considered a sensible choice of extrapolation for TTD based on the observed data.