

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Encorafenib plus cetuximab for previously
treated BRAF V600E mutation-positive
metastatic colorectal cancer**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using encorafenib with cetuximab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

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

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using encorafenib with cetuximab in the NHS in England.

For further details, see [NICE's guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 25 September 2020

Second appraisal committee meeting: 14 October 2020

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 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.
- 1.2 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.

Why the committee made these recommendations

Treatment for BRAF V600E mutation-positive metastatic colorectal cancer after previous systemic treatment includes combination chemotherapy, usually FOLFIRI (5-fluorouracil, folinic acid and irinotecan) followed by trifluridine–tipiracil then best supportive care. 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. However, these drug combinations are not used in NHS clinical practice. When evidence from other clinical trials is used to indirectly compare encorafenib plus cetuximab with FOLFIRI, and with trifluridine–tipiracil, the assumptions used make the results unreliable.

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.

Collecting further data is unlikely to address the clinical uncertainty. Also, with the current economic modelling, encorafenib plus cetuximab does not have potential to be cost effective compared with current treatment. So it cannot be recommended for use through the Cancer Drugs Fund.

2 Information about encorafenib

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). The CHMP adopted a new indication as follows: ‘in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy’. Because the marketing authorisation did not include triple therapy (encorafenib plus binimetinib and cetuximab), this appraisal only considers dual therapy.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

2.3 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. The size of the discount is commercial in confidence. It is the company’s responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Pierre Fabre Ltd, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

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.
- The company's amended cost for drugs at the start of the model cycle more accurately reflects costs in clinical practice.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report table 11, page 41), and took these into account in its decision making. It discussed the issues which were outstanding after the technical engagement stage.

The condition

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

3.1 Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer with a BRAF V600E mutation is a rare type of colorectal cancer. It is associated with a poorer prognosis and has a greater risk of recurring than colorectal cancer without the BRAF mutation. There has been little improvement in survival for BRAF V600E mutation-positive cancer despite improvements for colorectal cancer in general. 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.

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

3.2 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.

The treatment pathway

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

3.3 Encorafenib plus cetuximab has a marketing authorisation for treating metastatic colorectal cancer with a BRAF V600E mutation in people who have had previous systemic treatment. Current treatment options for this type of metastatic colorectal cancer include combination chemotherapy regimens, trifluridine–tipiracil and best supportive care. The committee noted that encorafenib plus cetuximab could be positioned at second line or later in the treatment pathway. The clinical experts explained that encorafenib plus cetuximab is the first targeted treatment for this population. The patient experts emphasised the psychological effect of being diagnosed with BRAF V600E mutation-positive metastatic colorectal cancer. They noted that using encorafenib plus cetuximab earlier in the

pathway could give people hope of improved outcomes and may avoid adverse events associated with current treatments. The committee recognised the clinical and patient experts' preference for using encorafenib plus cetuximab earlier in the treatment pathway. But it concluded that it may be used after 1 or more previous lines of treatment in clinical practice.

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

3.4 The clinical experts explained that treatment options for BRAF V600E mutation-positive metastatic colorectal cancer depend on the previous treatments a person has had, their response to these treatments, and their preferences. Most people have combination chemotherapy, usually folinic acid, fluorouracil (5-FU) and oxaliplatin (known as FOLFOX) first line followed by folinic acid, 5-FU and irinotecan (known as FOLFIRI). The clinical experts explained these treatments were interchangeable and considered equivalent. A small proportion of people have folinic acid, 5-FU, irinotecan and oxaliplatin (FOLFOXIRI) at first line, so would then have trifluridine–tipiracil as second-line treatment. The clinical experts noted that this was uncommon because of higher toxicity than with other combinations. The company explained that encorafenib plus cetuximab could be used instead of FOLFIRI or trifluridine–tipiracil after 1 previous line of treatment. The marketing authorisation for trifluridine–tipiracil allows for its use at second line and later. It is the only drug recommended after first-line treatment for metastatic colorectal cancer in the [NICE Pathway for colorectal cancer](#). However the committee recalled its conclusion in [NICE's technology appraisal guidance on trifluridine–tipiracil](#) that, in clinical practice, it would mainly be used in people who have had 2 or more previous lines of treatment when there are no further treatment options. The committee concluded that the relevant comparators after 1 previous line of treatment include both FOLFIRI and trifluridine–tipiracil.

Irinotecan monotherapy is not a relevant comparator for encorafenib plus cetuximab after 1 previous line of treatment

3.5 NICE's scope includes irinotecan monotherapy as a relevant comparator. However, the company excluded it based on expert opinion and a market survey which found that fewer than 2% of people have irinotecan monotherapy in clinical practice. This is because it is not well tolerated. The clinical experts agreed with the company and explained that in clinical practice irinotecan is used as part of FOLFIRI. When used with other treatments, the dose of irinotecan is lower and better tolerated. The clinical experts noted that irinotecan monotherapy is occasionally used when there is a specific intolerance to 5-FU or a dihydropyrimidine dehydrogenase deficiency resulting in an inability to detoxify 5-FU in the liver. The committee concluded that irinotecan monotherapy was not a relevant comparator after 1 previous line of treatment.

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

3.6 In clinical practice trifluridine–tipiracil is usually used after 2 previous lines of treatment. The clinical experts explained that it would be appropriate to use encorafenib plus cetuximab instead of trifluridine–tipiracil after 2 previous lines of treatment if neither had been used earlier in the treatment pathway. They explained that after trifluridine–tipiracil there are no other active treatment options and people would have best supportive care. The committee recognised that a small group of people with BRAF V600E positive mutations whose disease had relapsed after treatment with trifluridine–tipiracil may be eligible for encorafenib plus cetuximab. They would otherwise have best supportive care. 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 committee concluded that trifluridine–tipiracil and best supportive

care were relevant comparators for encorafenib plus cetuximab after 2 previous lines of treatment.

Clinical effectiveness of encorafenib plus cetuximab

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

3.7 BEACON CRC is a multinational, open-label, randomised, phase 3 trial comparing encorafenib plus cetuximab with the investigator's choice of chemotherapy (FOLFIRI or irinotecan) plus cetuximab. It included people with BRAF V600E mutation-positive metastatic colorectal cancer whose disease had progressed after 1 or 2 previous lines of treatment. The primary endpoints in the trial were for triple therapy (encorafenib plus binimetinib and cetuximab), which is not relevant for this appraisal. Overall survival, progression-free survival and overall response rate for encorafenib plus cetuximab were secondary endpoints. 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 5.1 months to 7.1 months). The associated hazard ratio was 0.61 (95% confidence interval 0.48 to 0.77). The committee concluded that encorafenib plus cetuximab prolonged survival, but noted that the comparators were not used in NHS clinical practice (see section 3.8).

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

3.8 The control arm of BEACON CRC does not reflect clinical practice in the NHS. This is because epidermal growth factor receptor (EGFR) inhibitors, such as cetuximab, are not recommended beyond first-line treatment for metastatic colorectal cancer in [NICE's technology appraisal guidance on cetuximab, bevacizumab and panitumumab](#). The clinical experts

explained that cetuximab is likely to have some benefit in people with BRAF V600E mutation-positive colorectal cancer who have not had an EGFR inhibitor before (included in BEACON CRC). However, how much benefit cetuximab has when used with FOLFIRI or irinotecan is unknown. The committee recognised that including cetuximab in the control arm of BEACON CRC meant that the trial results may underestimate the effect of encorafenib plus cetuximab. It concluded that the control arm of BEACON CRC does not reflect clinical practice and agreed to consider alternative estimates of relative efficacy in decision making.

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

3.9 Treatment in the control arm of BEACON CRC was not randomised, it was allocated according to the investigator's choice of irinotecan with cetuximab or FOLFIRI with cetuximab. The clinical experts explained that people are offered treatments depending on how their disease reacted to previous treatments, their comorbidities, and personal preference. The company said that about 40% of people in the control arm had irinotecan plus cetuximab. 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 committee considered that because of confounding, that is, factors associated with both the investigator's choice of treatment and with the patient's prognosis, it could not assume that irinotecan plus cetuximab was equivalent to FOLFIRI plus cetuximab. The committee concluded that the control arm does not reflect clinical practice because it included irinotecan and it should consider this in its decision making.

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

3.10 The company noted that people in BEACON CRC had a range of subsequent treatments after disease progression. The committee was aware that some of these treatments included immunotherapies, which

are not available at this point in the pathway in the NHS and may prolong life. The clinical experts explained that in current NHS clinical practice there are no active treatments after people have trifluridine–tipiracil. The committee appreciated 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. The company explained that it had not adjusted the trial results to take this into account. The committee concluded that the subsequent treatments in BEACON CRC did not reflect NHS clinical practice, which made generalising the overall survival results to NHS practice uncertain.

Analyses that adjust for the differences between the trial and clinical practice are needed

3.11 The committee noted that BEACON CRC differed from current NHS clinical practice because:

- cetuximab was included in the control arm of BEACON CRC (see section 3.8)
- factors influencing who has irinotecan plus cetuximab and who has FOLFIRI plus cetuximab affect clinical outcomes (see section 3.9)
- subsequent treatments in BEACON CRC did not reflect NHS clinical practice but may extend life (see section 3.10).

The committee concluded that BEACON CRC did not reflect clinical practice in the NHS so analyses that attempt to adjust for these issues are needed, but it acknowledged there is limited evidence for people with BRAF V600E mutation-positive metastatic colorectal cancer.

Indirect comparison of encorafenib plus cetuximab with FOLFIRI

Cetuximab and panitumumab are equally effective

3.12 The committee recalled that there were no data directly comparing encorafenib plus cetuximab with FOLFIRI, trifluridine–tipiracil or best supportive care. To estimate the relative efficacy of encorafenib plus

cetuximab compared with FOLFIRI, the company did an indirect treatment comparison using data from BEACON CRC and data from a subgroup of people with BRAF-positive metastatic colorectal cancer from Peeters et al. 2010 to 2015. Peeters et al. was a randomised controlled trial comparing FOLFIRI alone with FOLFIRI plus panitumumab in people with metastatic colorectal cancer. There were no common comparators between these 2 trials, so assumptions were needed. The control arm of BEACON CRC (investigator's choice of either FOLFIRI or irinotecan, both plus cetuximab) would have to be considered equivalent to the treatment arm in Peeters et al. (FOLFIRI plus panitumumab). The indirect treatment comparison was possible only by assuming equal efficacy for:

- cetuximab and panitumumab
- FOLFIRI and irinotecan.

The committee recalled the conclusion from [NICE's technology appraisal guidance on cetuximab and panitumumab](#) that cetuximab and panitumumab were likely to have similar effectiveness in treating RAS wild-type metastatic colorectal cancer. But the committee recognised that the population in this appraisal has the BRAF mutation. The clinical experts and NHS England's clinical lead for the Cancer Drugs Fund explained that cetuximab and panitumumab should be considered clinically equivalent in the population with BRAF mutation-positive disease, noting that there are differences in toxicity between the 2 drugs. The committee concluded that cetuximab and panitumumab were equally effective.

It is unclear whether FOLFIRI and irinotecan are equally effective, so the results of the indirect comparison are uncertain

3.13 The committee considered whether FOLFIRI and irinotecan were equally effective. The company cited data from 2 clinical trials to support this. The ERG highlighted that the trials were done in patients with unknown BRAF mutation status, so applying the results to this population increased the

uncertainty of the indirect treatment comparison. The committee was concerned that assuming equivalent effectiveness for FOLFIRI and irinotecan was unproven. It considered overall survival data from the BEACON CRC control arm split by treatment received (either irinotecan plus cetuximab or FOLFIRI plus cetuximab). It noted there were potential differences in outcomes between these treatment arms, but no formal statistical analysis had been done. The committee was aware of the lack of randomisation in the control arm and using the investigator's choice for the comparator treatment. It considered that there appeared to be differences in overall survival between the treatments, but this may be because of confounding (see section 3.9). The committee concluded that further analyses to justify similar efficacy for irinotecan and FOLFIRI in people with BRAF V600E mutation-positive disease would help reduce the uncertainty of this assumption. This should include a log-rank test to compare survival and analyses adjusted for potential confounders. The committee agreed that the evidence for equal effectiveness of FOLFIRI and irinotecan was uncertain, which made the results of the indirect treatment comparison uncertain.

Data from BEACON CRC and the indirect treatment comparison should be considered to compare encorafenib plus cetuximab with FOLFIRI

3.14 The committee recalled that the uncertainties associated with BEACON CRC meant the relative efficacy of encorafenib plus cetuximab compared with FOLFIRI could not be accurately estimated. However, it noted that the company's indirect treatment comparison was also highly uncertain. The ERG preferred to use the BEACON CRC data as a proxy for the clinical effectiveness of encorafenib with cetuximab compared with FOLFIRI. The committee considered that without an appropriate indirect treatment comparison, using randomised controlled trial evidence from BEACON CRC was preferable because it was less likely to be biased. But it noted that both approaches were uncertain, and concluded that it would take both into account in its decision making.

Clinical effectiveness of encorafenib plus cetuximab compared with trifluridine–tipiracil

It is appropriate to consider the RECURSE data as part of the clinical evidence

3.15 There were no studies for trifluridine–tipiracil with comparators common to the BEACON CRC trial. The company and ERG highlighted the lack of data for people with BRAF V600E mutation-positive colorectal cancer. The company identified the RECURSE trial, a randomised controlled phase 3 trial in people with metastatic colorectal cancer refractory or intolerant to standard therapies. It compared trifluridine–tipiracil with placebo, but noted that the population included people whose BRAF status was undefined. The company did a naive comparison using data from the trifluridine–tipiracil arm of RECURSE and from the encorafenib plus cetuximab arm of BEACON CRC. The company did not have access to individual patient level data from RECURSE, so instead simulated the data by digitalising the published survival curves. The committee understood the lack of data for this population. Although RECURSE included a highly heterogenous population compared with the BEACON CRC population, the committee concluded it was appropriate to consider as part of the clinical evidence.

The company’s naive comparison is uncertain

3.16 The committee recalled the considerable heterogeneity in potential prognostic factors between the study populations (BEACON CRC and RECURSE) included in the company’s naive comparison of encorafenib plus cetuximab with trifluridine–tipiracil. People in RECURSE had 4 or more previous lines of treatment compared with 1 or 2 previous lines of treatment in BEACON CRC. After technical engagement the company presented data from RECURSE, which suggested that outcomes were better for the population who had more lines of treatment. The company explained that this might be because those who have lived long enough to

have more lines of treatment may have better prognostic factors than those who have had fewer treatments. The clinical experts and company explained that in BEACON CRC, the number of previous treatments did not change the effect of encorafenib plus cetuximab. However, the committee noted that the population in RECURSE had not had testing for BRAF status. The company assumed that about 5% of the RECURSE trial population had BRAF V600E mutation-positive disease and noted the higher mortality associated with BRAF V600E mutation-positive colorectal cancer compared with wild-type colorectal cancer. To adjust for this, it applied a hazard ratio of 4.0 from Peeters et al. to survival outcomes. The company presented an alternative hazard ratio of 2.2 from a meta-analysis by Safaee (2012). The ERG presented estimates from MRC FOCUS (a UK randomised trial of 3 treatment strategies, including monotherapy and combination treatment with fluorouracil, irinotecan and oxaliplatin, hazard ratio 1.8). The committee agreed that it was appropriate to adjust for histology and other confounders, but noted the hazard ratios varied widely in the meta-analysis by Safaee. It was therefore not clear which hazard ratio provided an appropriate adjustment. The committee concluded that the company's naive comparison was uncertain.

The company's economic model

The company's model is appropriate for decision making

3.17 The company chose a partitioned survival model to estimate the cost effectiveness of encorafenib with cetuximab. The model included 3 health states: progression-free, progressed, and dead. The probability of being in a given health state was defined by the area under the curves for progression-free survival, overall survival, and their difference. The model cycle length was 1 month and the time horizon was 10 years. The committee considered the company's model to be appropriate for decision making.

Modelling overall survival

The most recent data cut from BEACON CRC should be used to model survival

3.18 The company provided an updated data cut (May 2020) from BEACON CRC after technical engagement. The data cut provided an additional 9 months of follow up after the trial had met its primary endpoint (see section 3.7). The ERG highlighted that the data cut was unplanned and, at the time of submission, subject to further validation and data cleaning. The ERG explained that the data could be biased in favour of encorafenib plus cetuximab. During the committee meeting the company confirmed that the updated data had been finalised and needed no changes. The committee considered that additional data on survival outcomes helped when considering the long-term extrapolations and agreed that it would take the updated data cut into consideration in its decision making.

Modelling overall survival for encorafenib plus cetuximab compared with FOLFIRI

A piecewise approach is preferred for modelling overall survival for encorafenib plus cetuximab

3.19 Follow up for BEACON CRC was short in relation to the modelled time horizon. So the company extrapolated the trial data for the encorafenib plus cetuximab arm, choosing a log-logistic distribution in its base case. The ERG noted that the log-logistic distribution provided the best statistical fit to the trial data, but other distributions had similar statistical fits and none of the distributions fitted the data well. It highlighted that the log-logistic hazard function was the most optimistic extrapolation. The committee observed that the hazard function for the BEACON CRC overall survival data showed a change in trajectory (slope of the line) for the hazard rate at 2.8 months. The clinical and patient experts explained that this may be because disease responds quickly in people who have encorafenib plus cetuximab. The clinical experts said that tumour marker

responses could be seen from as early as 2 weeks after treatment with encorafenib plus cetuximab. The committee was aware that the ERG preferred to fit the extrapolated curve from 2.8 months onwards, using the Kaplan–Meier data up to this point, rather than replacing the data with a model. The committee concluded that it was appropriate to model overall survival for encorafenib plus cetuximab using a piecewise approach.

Further exploration of modelling overall survival for encorafenib plus cetuximab is needed

3.20 Having concluded that a piecewise approach was the most appropriate method to model overall survival in the encorafenib plus cetuximab arm, the committee considered the alternative models used by the company and the ERG. The ERG chose the exponential distribution from 2.8 months onwards, but it was unable to provide updated analyses using the latest data cut (May 2020). The committee was aware that models are fitted to observed data, and that deciding whether extrapolations are plausible needs clinical input. The clinical experts explained that the exponential approach seemed pessimistic because it predicted that fewer people than expected would be alive after 5 years. After technical engagement the company provided 2 scenario analyses using piecewise curves, applying the log-logistic and the ERG-preferred exponential distributions to the updated May 2020 data cut. The committee noted that it had not been provided with results for other parametric curves. It would have preferred to have seen survival outcomes displayed visually for a variety of the extrapolations and the results of the statistical fit for the piecewise curves. The committee concluded that it would have preferred to see further exploration of piecewise approaches, using the May 2020 data cut and a variety of curve extrapolations.

The ERG's preferred approach is pessimistic and further exploration is needed to model overall survival for FOLFIRI

3.21 The committee recalled its earlier conclusion that both approaches to determine the relative effect of encorafenib plus cetuximab compared with

FOLFIRI were associated with uncertainties. It recalled its conclusion that the effect of treatment on clinical outcomes from the randomised trial was less likely to be biased. But, because the trial did not include a comparator that reflected NHS practice, it would take into account the indirect treatment comparison in its decision making. The company base case applied the hazard ratio 2.56 (95% confidence interval 1.23 to 5.26) from the indirect treatment comparison to the encorafenib plus cetuximab survival curves to generate survival curves for FOLFIRI. The company also provided a scenario analysis using parameterised curves for the Kaplan–Meier data from the control arm of BEACON CRC. The committee considered both approaches, along with the ERG’s preference of fitting a piecewise curve (see section 3.19) to the control arm of BEACON CRC. The clinical experts explained that survival for FOLFIRI is less than 10% at 3 years and 5% at 5 years. The committee concluded that the ERG’s preferred approach of using a piecewise curve and applying an exponential distribution seemed pessimistic. It agreed that further exploration of piecewise curves was needed to extrapolate overall survival for FOLFIRI.

Modelling progression-free survival

Kaplan–Meier data should be used to model progression-free survival

3.22 The company chose a jointly fitted parametric curve to extrapolate progression-free survival for encorafenib plus cetuximab. It applied the hazard ratio from the indirect treatment comparison to estimate the FOLFIRI survival outcomes (see section 3.16). The committee noted that none of the parametric models offered a good fit to the progression-free survival data in BEACON CRC. The ERG presented alternative analyses using the raw Kaplan–Meier data because this was relatively mature. The committee considered that it would be preferable to fit a curve to the data, but because this was not possible, using the Kaplan–Meier data was reasonable. It also noted that changes in how progression-free survival was modelled did not greatly affect the cost-effectiveness results. The

committee concluded that the Kaplan–Meier data should be used to model progression-free survival.

Modelling survival for encorafenib plus cetuximab compared with trifluridine–tipiracil

The cost effectiveness of encorafenib plus cetuximab compared with trifluridine–tipiracil would be very uncertain

3.23 Trifluridine–tipiracil is a relevant comparator at second and third line (see sections 3.4 and 3.6). BEACON CRC showed no difference in treatment effect for encorafenib plus cetuximab in people who had 1 or 2 previous lines of treatment. Therefore, the committee considered it reasonable to assume the same treatment effect for encorafenib plus cetuximab at second and third line. All the results of the company’s naive comparison were very uncertain (see section 3.16). The committee recalled that it would consider cost-effectiveness analyses that used a range of hazard ratios to adjust for differences in the populations between BEACON CRC and RECURSE, based on its earlier conclusion that the hazard ratios vary widely (see section 3.16). It concluded that the RECURSE overall survival curves should be adjusted to account for differences in BRAF mutation status, but that the cost-effectiveness results for encorafenib plus cetuximab compared with trifluridine–tipiracil would be very uncertain.

Subsequent treatments

Adjusting trial data for subsequent treatments not available in NHS practice is appropriate

3.24 The committee recalled that people in BEACON CRC had subsequent treatments that would not be available in NHS clinical practice and which might prolong life (see section 3.10). It was also aware that in the analysis these treatments affected costs in both treatment arms. The company did not attempt to adjust for the additional benefit or costs of these treatments. The committee considered it would be reasonable to adjust for

subsequent treatments not available in the NHS and which may prolong life.

Waning of treatment effect

It is appropriate that the model does not include waning of the treatment effect

3.25 The company's model assumed that the relative survival benefit of encorafenib plus cetuximab, compared with current treatment, was maintained at the same level for the rest of a person's life if they remained in the pre-progression health state. The committee was aware that neither the company nor the ERG had modelled scenarios in which the treatment benefit in the extrapolated phase diminishes in the long term. The clinical experts explained that the benefit of encorafenib plus cetuximab is likely to continue while the person is having treatment and noted there is no stopping rule for the treatment. The committee accepted the clinical experts' comments and concluded that the company's model need not include waning of the relative treatment effect.

Utility values in the economic model

The utility estimates in the company's model are appropriate

3.26 BEACON CRC included the EQ-5D-5L health questionnaire to measure health-related quality of life. The company mapped the EQ-5D-5L data to the EQ-5D-3L to estimate mean utility for the pre-progressed and progressed disease health states in line with [NICE's methods guide](#). After technical engagement the company applied a utility value from only those people who had FOLFIRI (plus cetuximab) in the clinical trial to people who had FOLFIRI in the model. The committee noted that the utility value used for the post-progression health state in the encorafenib plus cetuximab arm was slightly lower than for the FOLFIRI arm. The company explained that although these were different in the modelling, the range of the utilities in each arm overlapped and were not statistically different. The

ERG also highlighted that the utility values were not collected at the same time point in each arm, which may have affected the results. The committee considered it reasonable that the health utility data collected in BEACON CRC would capture decrements for adverse events because they were treatment specific. The committee concluded that the utility estimates used in the company's model were appropriate.

Costs in the economic model

Time to treatment discontinuation should be applied in the model

3.27 Time to treatment discontinuation determines total acquisition costs for a treatment. The company instead used time to disease progression, assuming that time to treatment discontinuation was equivalent to progression-free survival. The company's clinical experts supported this assumption. The company explained that it used progression-free survival to model time to treatment discontinuation because the trials used in the indirect and naive treatment comparison did not report time to treatment discontinuation. It provided a scenario analysis using time to treatment discontinuation for encorafenib with cetuximab which lowered the treatment costs. The committee considered that there was some uncertainty around the most plausible model to estimate time on treatment and further analyses were needed to explore the effect on the incremental cost-effectiveness ratio (ICER). But it preferred using time to treatment discontinuation in the economic model.

It is appropriate to use mean relative dose intensities in the model

3.28 The company used mean relative dose intensities, that is, the ratio of the given dose to the planned dose, in the economic model. The ERG explained its preference for using median values because the trial data are skewed, meaning that the median is higher than the mean. It noted that this may be caused by some poor outcomes early in the trial. The company explained that it used the mean because it better reflected what

will happen in clinical practice. The committee concluded that mean relative dose intensities should be used in the model.

It is appropriate to assume 10% drug wastage for oral treatments

3.29 In its base case, the company assumed sharing vials and no wastage. It provided a scenario analysis that assumed vial wastage occurs in 10% of dispensed drugs. The clinical lead for the Cancer Drugs Fund explained that it was reasonable to assume 10% drug wastage for oral drugs because people may stop taking treatment between clinic visits. But assuming no drug wastage for intravenous drugs would be appropriate because cetuximab and FOLFIRI are common treatments used in the NHS with relatively long shelf lives. The committee concluded that 10% drug wastage for oral treatments should be assumed in the economic model.

End of life

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

3.30 The committee considered the advice about life-extending treatments for people with a short life expectancy in [NICE's guide to the methods of technology appraisal](#). 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 committee noted that the median overall survival for the control arm in BEACON CRC was 5.9 months and the literature suggested that median survival for people with BRAF V600E mutation-positive colorectal cancer was shorter than 12 months. The committee recognised that the mean values would be higher but would likely remain below 2 years. The committee thought it was plausible that encorafenib plus cetuximab would result in a survival gain of more than 3 months compared with standard care despite limitations in the comparative evidence base. The median overall survival gain in BEACON CRC was 3.4 months for encorafenib plus cetuximab

compared with the investigator's choice. Both the ERG's and the company's modelling estimated a survival gain of more than 3 months. The committee concluded that encorafenib plus cetuximab met the criteria to be considered a life-extending end of life treatment.

Innovation

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

3.31 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.

Cost-effectiveness estimate

It is appropriate to make pairwise comparisons rather than incremental analyses

3.32 Because of confidential commercial arrangements for encorafenib and cetuximab, none of the cost-effectiveness results are reported here. The committee recalled that the second-line comparators depended on the person's previous treatment, so they reflected distinct populations which made pairwise comparisons appropriate.

Encorafenib plus cetuximab is effective and innovative but the cost-effectiveness estimates do not reflect the preferred modelling

3.33 The committee noted the high level of uncertainty with the clinical and modelling assumptions made by the company and the ERG, specifically:

- The control arm of BEACON CRC did not reflect NHS clinical practice (see section 3.8).
- There were no head-to-head trials comparing encorafenib plus cetuximab with FOLFIRI or with trifluridine–tipiracil (see section 3.12).
- The company’s indirect treatment comparison made several uncertain clinical assumptions, including that FOLFIRI and irinotecan are clinically equivalent (see sections 3.12 and 3.13).
- The results of the company’s naive comparison were uncertain (see section 3.16).
- The analysis does not take into account subsequent treatments used in the trial but not available in the NHS (see section 3.10).

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.

The committee would prefer to see analyses with its preferred assumptions

3.34 Because none of the company’s or the ERG’s analyses reflected the committee’s preferences, it would have preferred to see the following information.

The indirect treatment comparison:

- Analyses from the control arm of BEACON CRC split by treatment (FOLFIRI plus cetuximab or irinotecan plus cetuximab; see section 3.13) including:

- adjustment for potential confounders
- a log-rank test to assess the overall and progression-free survival.

Modelling of encorafenib plus cetuximab and of FOLFIRI:

- Cost-effectiveness results using the clinical efficacy data from BEACON CRC (see section 3.20).
- Cost-effectiveness results using the hazard ratio from the indirect treatment comparison applied to survival outcomes to adjust for the presence of cetuximab (see section 3.21).
- Cost-effectiveness results using the May 2020 data cut from BEACON CRC (see section 3.18).
- A full range of piecewise extrapolations for estimating overall survival of encorafenib plus cetuximab and of FOLFIRI (see 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 sections 3.10 and 3.24).
- Cost-effectiveness results using Kaplan–Meier data from BEACON CRC to model progression-free survival (see section 3.22).

Modelling of encorafenib plus cetuximab and trifluridine–tipiracil:

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

Cost estimates in the modelling:

- Cost-effectiveness results applying 10% drug wastage for oral treatments (see section 3.29).
- Cost-effectiveness results using time to treatment discontinuation (see section 3.27).

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 (see section 3.6).

Encorafenib with cetuximab is not recommended in the NHS

3.35 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.

Cancer Drugs Fund

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

3.36 Having concluded that encorafenib plus cetuximab could not be recommended for routine use, the committee then considered if it could be recommended for previously treated BRAF V600E mutation-positive metastatic colorectal cancer within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting [NICE's Cancer Drugs Fund methods guide \(addendum\)](#). The committee noted that the company did not express an interest in the treatment being considered for funding through the Cancer Drugs Fund. The committee noted that BEACON CRC had met its primary endpoint and that the company had provided further, more mature, 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. The committee noted that it had not seen cost-effectiveness estimates reflecting its preferred modelling. The current estimates for encorafenib plus cetuximab did not have plausible

potential to be cost effective compared with current treatment (see section 3.33). Therefore, the committee did not recommend encorafenib with cetuximab for use in the Cancer Drugs Fund.

Equalities

There are no equalities issues identified for encorafenib plus cetuximab

3.37 No equalities issues were identified during scoping, submission or technical engagement. The committee concluded that there were no equalities issues for treatment with encorafenib plus cetuximab.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
September 2020

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Jessica Cronshaw

Technical lead

Lorna Dunning

Technical adviser

Jo Ekeledo

Project manager

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