

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final appraisal document**

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

**1 Recommendations**

- 1.1 Encorafenib plus cetuximab is recommended, within its marketing authorisation, as an option for treating BRAF V600E mutation-positive metastatic colorectal cancer in adults who have had previous systemic treatment. It is recommended only if the company provides it according to the commercial arrangements (see section 2).

**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 second or third line.

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, because NICE does not recommend cetuximab beyond first-line treatment for metastatic colorectal cancer. Assumptions are needed to indirectly compare encorafenib plus cetuximab with FOLFIRI or trifluridine–tipiracil using evidence from other clinical trials. This make the results uncertain.

Encorafenib plus cetuximab meets NICE's criteria for being a life-extending treatment at the end of life. Also, despite the uncertain comparative effectiveness results, the cost-effectiveness estimates are within what is normally considered a cost-effective use of NHS resources. So, it is recommended for routine use in the NHS.

## 2 Information about encorafenib plus cetuximab

### Marketing authorisation indication

2.1 Encorafenib (Braftovi; Pierre Fabre Ltd) has a marketing authorisation in combination with cetuximab (Erbix; Merck Serano Ltd) 'for the treatment of adult patients with metastatic colorectal cancer (CRC) 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 October 2020).

The list price of cetuximab 5 mg per millilitre solution for infusion is £890.50 for 100 millilitres (excluding VAT; BNF online accessed October 2020).

The companies have commercial arrangements for each of the drugs. These make encorafenib and cetuximab available to the NHS with discounts. The size of the discounts is commercial in confidence. It is the companies' responsibility to let relevant NHS organisations know details of the discounts.

### 3 Committee discussion

The [appraisal committee](#) 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 that 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). BRAF is a human gene that encodes the protein B-Raf, which influences cell growth. 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 that 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. They explained that their cancers 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 had improved enormously because the adverse effects of this therapy 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**

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 NHS 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 second line or later in the treatment pathway. The clinical experts explained that encorafenib plus cetuximab is the first targeted treatment for this population, and their preference for using it after first-line treatment. 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 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. The committee 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 that these treatments are interchangeable and considered equivalent. A small proportion of people have folinic acid, 5-FU, irinotecan and oxaliplatin (FOLFOXIRI) first line, so would then have trifluridine–tipiracil as second-line treatment. The clinical experts noted that this was uncommon because of the higher toxicity with FOLFOXIRI 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 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. 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 than when used as monotherapy. 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 is not a relevant comparator after 1 previous line of treatment.

### **Trifluridine–tipiracil is a relevant comparator 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. The committee concluded that trifluridine–tipiracil is a relevant comparator for encorafenib plus cetuximab after 2 previous lines of treatment.

### **Best supportive care is not a relevant comparator for encorafenib plus cetuximab**

3.7 NICE’s scope for the appraisal included best supportive care as a relevant comparator. After treatment with trifluridine–tipiracil, there are no other active treatment options and people 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. The clinical experts agreed that encorafenib plus cetuximab could also be used when no other active treatment options are available. However, they noted that, at this stage, people may not be well enough to have active treatment. The company and ERG agreed that patients eligible for best supportive care would generally not be well enough to have active treatment, including encorafenib plus cetuximab. The committee concluded that best supportive care was not a relevant comparator for encorafenib plus cetuximab.

## **Clinical effectiveness of encorafenib plus cetuximab**

### **Encorafenib plus cetuximab is clinically effective based on BEACON CRC but the comparators in the trial are not used in the NHS**

3.8 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 compared with controls were secondary endpoints. Results showed that encorafenib plus cetuximab increased overall survival more than the investigator's choice of either FOLFIRI plus cetuximab or irinotecan plus cetuximab. The clinical experts explained that the control arm of BEACON CRC did 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](#). In addition, about 40% of

people in the control arm had irinotecan plus cetuximab. The committee recalled that irinotecan monotherapy is not a relevant comparator because it is associated with worse toxicity than FOLFIRI (see section 3.5). It heard that irinotecan monotherapy would not be offered second line with cetuximab. The committee concluded that encorafenib plus cetuximab is clinically effective compared with the comparators in the trial, but these treatments do not reflect NHS clinical practice.

**Cetuximab likely benefits patients so the trial may underestimate the relative effect of encorafenib plus cetuximab compared with FOLFIRI**

3.9 The committee recalled that cetuximab is not recommended in the NHS beyond first-line treatment for metastatic colorectal cancer. However, the clinical experts at the first committee meeting explained that it is likely to benefit people with BRAF V600E mutation-positive colorectal cancer who have not had an EGFR inhibitor. However, they also noted that there are limited data available for this population, so how much benefit cetuximab has when used with FOLFIRI or irinotecan is unknown. At consultation after the first committee meeting, a consultee cited data from CRYSTAL. This was a randomised controlled phase 3 study comparing cetuximab plus FOLFIRI with FOLFIRI first line in people with KRAS wild-type metastatic colorectal cancer, and in people with known BRAF V600E mutations. Results showed that both populations had improved survival when FOLFIRI was used with cetuximab compared with FOLFIRI alone. The committee recognised that the CRYSTAL study included people who had not had prior treatment. However, the clinical experts and the NHS England lead for the Cancer Drugs Fund explained that the population seen in the NHS would not have had an EGFR inhibitor before. This meant that they would be likely to have a similar benefit to that seen in CRYSTAL. The committee concluded that cetuximab was likely to have added benefit to FOLFIRI and irinotecan in the control arm of BEACON CRC. This meant that the BEACON CRC trial results may have underestimated the relative effectiveness of encorafenib plus cetuximab



compared with FOLFIRI alone. It agreed to consider this in its decision making.

### **Irinotecan may not be clinically equivalent to FOLFIRI**

3.10 Treatment in the control arm of BEACON CRC included either FOLFIRI plus cetuximab or irinotecan plus cetuximab. The committee appreciated that if irinotecan and FOLFIRI are equally effective, then it would be satisfied that irinotecan plus cetuximab and FOLFIRI plus cetuximab are also equally effective. The committee was aware that treatment in the control arm was not randomised. Instead, it was allocated according to the investigator's choice, which the committee recognised was a 'blended comparator'. The clinical experts explained that people are offered treatments depending on how their disease reacted to previous treatments, their comorbidities, and personal preference. The committee recalled that 40% of people in the control arm had irinotecan plus cetuximab. It 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 the results may not apply in this population. In its first meeting, the committee was concerned that assuming equivalent effectiveness for FOLFIRI and irinotecan was unproven. At consultation, the company presented results from a stratified log-rank test. The committee was aware that the trial was not powered to detect differences in survival for the control arm but noted that the results showed worse survival for people in the BEACON CRC trial who had irinotecan plus cetuximab compared with FOLFIRI plus cetuximab, although the results were uncertain. The ERG noted that the results included the possibility of no difference. The committee was aware of the possibility of confounding by indication. So, it considered the company's multivariate Cox analysis controlling for age, sex, characteristics of the tumour, number of organs involved and prior use of oxaloplatin. This analysis also showed a hazard ratio indicating that patients taking irinotecan plus cetuximab died earlier than those taking FOLFIRI plus cetuximab. The committee noted that

these results were uncertain and included the possibility of no difference. The company noted that there were no covariates excluded from the multivariable analysis. The clinical experts explained that most oncologists would view the 2 treatments as having similar efficacy. Also, 1 consultee explained that FOLFIRI is better tolerated. One expert noted that there will likely be clinical reasons (for example, 5-FU intolerance or not wanting an implanted venous access device necessary to deliver FOLFIRI) as to why investigators chose irinotecan over FOLFIRI. The committee was aware of the lack of evidence for people with BRAF mutations. However, it concluded that irinotecan may not be equivalent to FOLFIRI and took this into consideration in its decision making.

### **Comparing encorafenib plus cetuximab with the blended comparators from BEACON does not reflect the comparison with FOLFIRI**

3.11 The BEACON control arm included investigators choice plus cetuximab. Investigators choice included either FOLFIRI or irinotecan. The committee appreciated that the components of the blended comparator have different degrees of benefit, and that this approach averages the clinical effectiveness of the treatments included. It recalled its conclusion that cetuximab is likely to add benefit to FOLFIRI alone, but also that irinotecan is associated with worse toxicity and potentially poorer outcomes than FOLFIRI (see section 3.10). The committee concluded that including a blended comparator in the estimates of clinical effectiveness does not reflect the comparison with FOLFIRI.

### **Indirect comparison of encorafenib plus cetuximab with FOLFIRI**

#### **The indirect comparison of encorafenib plus cetuximab with FOLFIRI is useful for decision making**

3.12 Analyses that adjust for the differences between the trial and clinical practice should inform decision making. The committee noted that BEACON CRC differed from current NHS clinical practice because:

- irinotecan was included in the control arm of the trial (see section 3.8)
- cetuximab was added to irinotecan and FOLFIRI, which added benefit (see section 3.9)
- irinotecan may not be clinically equivalent to FOLFIRI (see section 3.10)
- the blended comparators make the relative effectiveness analyses uncertain (see section 3.11).

The committee concluded that BEACON CRC did not reflect the comparison with FOLFIRI. In addition, it concluded that it would take into account the company's indirect comparison of encorafenib plus cetuximab with FOLFIRI to inform decision making.

### **Cetuximab and panitumumab are equally effective**

3.13 The committee recalled that there were no data directly comparing encorafenib plus cetuximab with FOLFIRI or trifluridine–tipiracil. 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 to form a network. 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) to form a network. 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. 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. The committee concluded that cetuximab and panitumumab were equally effective.

### **The results of the indirect comparison are uncertain because FOLFIRI and irinotecan may not be equally effective**

3.14 The committee recalled its conclusion that FOLFIRI and irinotecan may not be equally effective (see section 3.10). It noted that an assumption of equivalence was needed to estimate the relative effectiveness of encorafenib plus cetuximab with FOLFIRI using both the BEACON CRC results and the alternative analyses. The committee concluded that the evidence for equal effectiveness of FOLFIRI and irinotecan was uncertain, which made the results of the indirect treatment comparison uncertain.

### **All estimates of relative effectiveness for encorafenib plus cetuximab compared with FOLFIRI are uncertain**

3.15 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 plus cetuximab compared with FOLFIRI, and provided scenarios adjusting for cetuximab's duration of effect. The committee concluded that all relative effectiveness results were uncertain and it would consider this in its decision making.

## **Clinical effectiveness of encorafenib plus cetuximab compared with trifluridine–tipiracil**

### **The RECURSE trial contributes relevant clinical evidence**

3.16 There were no studies for trifluridine–tipiracil with comparators common to BEACON CRC. 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 refractory metastatic colorectal cancer or who could not tolerate standard therapies. It compared trifluridine–tipiracil with placebo, but the company 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 that there was a lack of data for this population. Although RECURSE included a highly heterogenous population compared with the BEACON CRC population, the committee concluded that it was appropriate and relevant to consider as part of the clinical evidence.

### **The company’s naive comparison of encorafenib plus cetuximab with trifluridine–tipiracil is uncertain**

3.17 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 people who had more lines of treatment compared with those

who had fewer lines of treatment. The clinical experts and company explained that, in BEACON CRC, the number of previous treatments was not associated with 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. It also noted the higher mortality associated with BRAF V600E mutation-positive colorectal cancer compared with wild-type colorectal cancer. To adjust the baseline hazard (poorer outcomes for those with BRAF mutation), it applied a hazard ratio to survival outcomes. At the first meeting, the committee concluded that it was appropriate to adjust survival for poorer outcomes in the BRAF population but that the appropriate hazard ratio was uncertain. At consultation, the company amended its choice of hazard ratio from 4.0 to 2.2. It noted that the updated value of 2.2 was derived from a meta-analysis (Safaei et al. 2012) including multiple studies identified by systematic review. The company suggested that it was therefore likely to be more reliable than a single study result. Alternative scenarios were presented by the ERG, which adjusted the baseline mortality using a hazard ratio of 1.8 from MRC Focus (2009). This was a UK randomised trial among people with advanced colorectal cancer who had 1 of 3 treatment strategies, including monotherapy and combination treatment with fluorouracil, irinotecan and oxaliplatin. In addition, the ERG presented an unadjusted analysis that did not adjust for the presence of a BRAF mutation (that is, it naively compared encorafenib plus cetuximab with the intervention arm of RECURSE). The clinical experts expected survival to be much lower for people who had trifluridine–tipiracil if they had a BRAF V600E mutation than for those with no BRAF V600E mutation. The committee agreed that it was appropriate to adjust for histology because all studies showed poorer outcomes for people with the BRAF V600E mutation. However, it also thought it important to consider other potential confounders. The committee noted that there was considerable range in the hazard ratios

provided to adjust survival outcomes for the presence of BRAF mutations. It concluded that the meta-analysis (Safaei et al. 2012) was likely to provide the most reliable hazard ratio.

## **Subsequent treatments in BEACON CRC**

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

3.18 In the first committee meeting 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 had 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. At consultation, the company noted that it was unable to adjust survival outcomes for subsequent treatments but provided details of subsequent treatments by trial arm. Consultees explained that subsequent therapies were unlikely to have prolonged life in the encorafenib plus cetuximab arm. The clinical experts noted that more patients in the control arm of BEACON CRC had had BRAF inhibitors as subsequent therapies, which may have improved survival. So, the effect of encorafenib plus cetuximab may have been underestimated. The committee noted that it would have preferred to see analyses controlling for the effect of subsequent treatments. Nevertheless, it concluded that subsequent treatments were unlikely to have had a large effect on the survival estimates.

## **The company's economic model**

### **The company's model is appropriate for decision making**

3.19 The company chose a partitioned survival model to estimate the cost effectiveness of encorafenib plus cetuximab. The model included 3 health states reflecting colorectal cancer: 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**

3.20 The company provided an updated data cut (May 2020) from BEACON CRC after technical engagement, which provided an additional 9 months of follow up. The committee considered that additional data on survival outcomes helped when considering the long-term extrapolations, and agreed that it would consider the updated data cut 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**

3.21 Follow up for BEACON CRC was short in relation to the modelled time horizon. 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



fitted the data well. The committee noted 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 have been because disease responds quickly to encorafenib plus cetuximab. The clinical experts said that responses in tumour markers 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 observed Kaplan–Meier data from the trial up to this point, using a ‘piecewise’ approach. The committee considered that it was appropriate to model overall survival for encorafenib plus cetuximab using a piecewise approach.

### **The generalised gamma distribution should be used to model overall survival for encorafenib plus cetuximab**

3.22 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 models used by the company and the ERG. At consultation, the company chose the log-logistic model distribution from 2.8 months onwards based on statistical fit. The committee was aware that statistical fit considers only the time period in which the models are fitted to the observed data. It noted the ERG’s statements that there were low numbers of people in the trials at risk towards the tail of the Kaplan–Meier curve, and that deciding whether extrapolations are plausible needs clinical input. The ERG highlighted that it was difficult to distinguish between the parametric curves by looking at them, and the 10-year survival proportions were not negligible for many of the curves. The clinical experts explained that the log-logistic curve could plausibly reflect mortality. However, they pointed out that it represented the upper-bound expected for overall survival. This was because a higher proportion of people than expected were predicted to be alive at 10 years. The committee considered that the Weibull distribution represented the lower-bound of plausible approaches. It concluded that the generalised gamma

curve lay between the 2 and most closely reflected what clinical experts expected in clinical practice. It further concluded that the generalised gamma curve, fitted using a piecewise approach, was the most appropriate for extrapolating overall survival.

### **Estimates of overall survival for FOLFIRI likely lie between the BEACON CRC control arm and the company's indirect treatment comparison**

3.23 The committee recalled its conclusion that all estimates of relative effectiveness for encorafenib plus cetuximab compared with FOLFIRI were associated with uncertainties (see section 3.15). At consultation, the company provided updated analyses using the May 2020 data cut from BEACON CRC. The company applied a hazard ratio of 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 ERG provided scenario analyses that explored the duration of cetuximab effect from none (reflecting use of the BEACON CRC control arm as a proxy for FOLFIRI) to lifetime (reflecting adjustment using the company's indirect treatment comparison). The committee also considered a result from an alternative scenario that used data from the CRYSTAL study (see section 3.9) to provide an indirect treatment comparison. Survival estimates using CRYSTAL data were lower than those from BEACON CRC, but above those of the company's original base case using the indirect treatment comparison. The clinical experts expected survival to be low for people who had FOLFIRI alone, with no one alive at 5 years and fewer than 2% alive at 3 years. The committee noted that results from the indirect treatment comparison and ERG scenario analyses best reflected these estimates. It also noted the preference to use the same hazard function for both treatment arms, which was consistent with the recommendations from NICE's Decision Support Unit. The committee therefore preferred extrapolating with the generalised gamma distribution to compare encorafenib plus cetuximab with FOLFIRI. It concluded that the comparator arm of BEACON CRC needed adjustment for the benefit associated with cetuximab. It further

concluded that the most plausible survival estimates for FOLFIRI were likely to lie between the company's indirect treatment comparison and the BEACON CRC control arm.

## **Modelling progression-free survival**

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

3.24 In the company's original submission, a jointly fitted parametric curve was chosen to extrapolate progression-free survival for encorafenib plus cetuximab. The company applied the hazard ratio from the indirect treatment comparison to estimate the FOLFIRI survival outcomes (see section 3.13). 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 these were 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. At consultation, the company updated its base case to use observed Kaplan–Meier data to model progression-free survival for encorafenib plus cetuximab, but noted that this was not possible for FOLFIRI or trifluridine–tipiracil. The committee concluded that the Kaplan–Meier data should have been used to model progression-free survival if possible. However, it did not think that not doing this had a large effect on the cost-effectiveness results.

## **Modelling overall survival for encorafenib plus cetuximab compared with trifluridine–tipiracil**

### **To estimate cost effectiveness the generalised gamma curve adjusted to account for differences in BRAF mutation status is the most appropriate**

3.25 Trifluridine–tipiracil is a relevant comparator for second and third-line treatment (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 3.17). 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 REOURSE, based on its earlier conclusion that the hazard ratios vary widely (see section 3.17). It considered the different approaches to extrapolating the curves. It recalled that the generalised gamma curve was the best fit for encorafenib plus cetuximab (see section 3.22), and that the same extrapolation should apply for the comparator arm in line with the NICE Decision Support Unit recommendation. It concluded that the most appropriate curve fit was generalised gamma, and that the REOURSE overall survival curves should be adjusted to account for differences in BRAF mutation status.

## **Subsequent treatments**

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

3.26 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 3.18). 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 survival benefit. However, it did provide a scenario accounting for the costs of these treatments. The committee considered that this scenario did not have a large effect on the incremental cost-effectiveness ratio (ICER). Also, it recalled that any survival gain caused by subsequent treatment was likely to lengthen the life of patients in the control arm more than the encorafenib arm (see section 3.18). The committee concluded that subsequent treatments in BEACON CRC were unlikely to have a big effect on the results of the cost-effectiveness analyses.

## Waning of treatment effect

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

3.27 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 a person 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 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. They also noted that 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

3.28 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 those people who had FOLFIRI plus cetuximab in the clinical trial to people who had FOLFIRI only in the model. The committee noted that the utility value used by the company 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. 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 captured 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**

3.29 Time to treatment discontinuation determines total acquisition costs for a treatment. At consultation, the company provided scenarios using time to treatment discontinuation for comparisons using the BEACON CRC control arm as a proxy for FOLFIRI. In all other analyses, the company assumed that time to treatment discontinuation was equivalent to progression-free survival. 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 comparisons did not report time to treatment discontinuation. The ERG highlighted that using time to treatment discontinuation had a bigger effect on encorafenib plus cetuximab costs than on comparator costs. It also explained that time to treatment discontinuation was available for encorafenib plus cetuximab, so it should have been applied to the treatment arm. The ERG's scenarios applied time to treatment discontinuation to the encorafenib plus cetuximab arm, and made assumptions to include time to treatment discontinuation in the comparator arms. The committee concluded that the ERG's scenarios using time to treatment discontinuation were appropriate for decision making.

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

3.30 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 have been 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**

3.31 In its base case, the company assumed sharing vials and no wastage. It provided a scenario analysis that assumed that 10% of patients would waste some tablets in a pack by rounding up to the nearest whole pack. 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 ERG explained that the company wastage scenario did not reflect 10% wastage, because it assumed only 10% of patients waste tablets, rather than all patients waste 10% of tablets. It presented scenario analyses that increased the encorafenib costs by 10% to account for wastage. The committee concluded that the ERG's scenario more accurately represented 10% drug wastage.

## **End of life**

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

3.32 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 that 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 than the median, 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**

3.33 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 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 targets for other treatment options in the future. The committee noted that the treatment is not a chemotherapy and may transform people's quality of life. The committee concluded that encorafenib plus cetuximab is an innovative treatment for BRAF V600E mutation-positive colorectal cancer.

## **Cost-effectiveness estimate**

### **It is appropriate to make pairwise comparisons rather than incremental analyses**

3.34 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 reflected distinct populations, which made pairwise comparisons appropriate.

### **Encorafenib plus cetuximab is effective and innovative, but the cost-effectiveness estimates are uncertain**

3.35 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 sections 3.12 and 3.16).
- The company's indirect treatment comparison made several uncertain clinical assumptions, including that FOLFIRI and irinotecan are clinically equivalent (see sections 3.13 and 3.14).
- The results of the company's naive comparison were uncertain (see section 3.17).
- The analysis does not take into account subsequent treatments used in the trial but not available in the NHS (see section 3.18).

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 the cost-effectiveness estimates were uncertain.

### **Encorafenib plus cetuximab is recommended in the NHS**

3.36 Because of the level of uncertainty in the clinical evidence, the committee recalled that all the cost-effectiveness results were uncertain. However, it agreed that the most plausible ICER was within what NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. It therefore concluded that it could recommend

encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive colorectal cancer for routine commissioning.

## Equalities

### No equalities issues were identified for encorafenib plus cetuximab

3.37 At consultation, several web comments were received stating that the draft guidance discriminated against young people. This was because the average age of patients in BEACON CRC was 60 years, which does not reflect the younger population who would be eligible to have encorafenib plus cetuximab. 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. They noted that this population would be well enough to have chemotherapy and encorafenib plus cetuximab. The committee was aware that its recommendation applied to everyone covered by 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. The committee concluded that there were no equalities issues for treatment with encorafenib plus cetuximab.

## 4 Implementation

4.1 [Section 7\(6\) of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be

available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously treated BRAF V600E mutation-positive metastatic colorectal cancer and the doctor responsible for their care thinks that encorafenib plus cetuximab is the right treatment, it should be available for use, in line with NICE’s recommendations.

## **5 Review of guidance**

- 5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Amanda Adler  
Chair, appraisal committee  
November 2020

## **6 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

ISBN: [to be added at publication]