Economic evaluation of encorafenib with cetuximab in patients with BRAF V600E-mutant metastatic colorectal cancer in France: a cost-effectiveness analysis using data from the BEACON CRC randomised controlled trial

Jean-Baptiste Trouiller, Bérengère Macabeo, Andrew Poll, Dan Howard, Andy Buckland, Marine Sivignon, Emilie Clay, David Malka, Emmanuelle Samalin, Mondher Toumi, Philippe Laramée

ABSTRACT

Objective The BEACON CRC randomised controlled trial (NCT02928224) in BRAF-mutant metastatic colorectal cancer (mCRC) patients showed improved overall survival for the combination treatment of encorafenib (BRAF inhibitor) with cetuximab (EGFR inhibitor) compared with cetuximab with chemotherapy (FOLFIRI (folinic acid, fluorouracil and irinotecan) or irinotecan). We aimed to evaluate the cost-effectiveness of encorafenib with cetuximab in adult patients with BRAF-mutant mCRC after prior systemic therapy, from the perspective of the French healthcare system.

Design A partitioned survival analysis model was developed to assess the cost-effectiveness of encorafenib with cetuximab using data from BEACON CRC (encorafenib with cetuximab and cetuximab with FOLFIRI or irinotecan). For two further comparator treatments (FOLFIRI alone and bevacizumab with FOLFIRI), a systemic literature review identified appropriate clinical trial data for indirect comparison. Piecewise modelling extrapolation was used to fulfill a lifetime horizon in the model. A discount rate of 2.5% was used. Treatment-emergent adverse events grade 3 with an incidence of ≥2% were included, as well as relative dose intensity and utility values.

Outcome measures The effectiveness outcomes of the model were expressed in terms of incremental life years gained and incremental quality-adjusted life years (QALY) gained. The cost-effectiveness of encorafenib with cetuximab was assessed using the incremental cost-effectiveness ratio (ICER). Results were presented probabilistically to account for parametric uncertainty. Deterministic and scenario analyses were conducted.

Results The ICER for encorafenib with cetuximab versus cetuximab with FOLFIRI or irinotecan, FOLFIRI alone and bevacizumab with FOLFIRI was €69 823/QALY, €70 421/QALY and €72 336/QALY, respectively. Encorafenib with cetuximab was considered cost-effective compared with the three comparators at a willingness to pay threshold of €90 000/QALY, with probabilities of being cost-effective of 89.8%, 98.2% and 86.4%, respectively.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Cost-effectiveness analysis developed using the most widely accepted modelling approach in oncology, in alignment with standard modelling practices, with inclusion of uncertainty and robustness assessment.

⇒ Inclusion of long-term overall survival data from a phase 3 randomised controlled trial as well as utilities and resource use data from the same trial, the latter adjusted as appropriate to the perspective of analyses.

⇒ External validation of the overall survival modelling, which uses a piecewise approach to accurately reflect the randomised controlled trial data.

⇒ Conduct of a systematic literature review to include data for comparator treatments that were not assessed by the source trial.

⇒ Paucity of comparative data in BRAF-mutant metastatic colorectal cancer patients, meaning assumptions were necessary for certain comparisons with treatments not assessed by the source trial, and potentially limiting the generalisability of the analysis to the real-world setting.

Conclusions This analysis showed encorafenib with cetuximab to be a cost-effective treatment in mCRC patients with a BRAF V600E mutation.

INTRODUCTION

In the European Union (EU), colorectal cancer (CRC) is the second most common cancer and the second leading cause of cancer deaths. In terms of direct costs, CRC is the second most expensive cancer in the EU, with an annual cost estimate of €5.57 billion. At a societal level, CRC is estimated to represent a cost of €13.1 billion to the EU, accounting...
for 10% of overall cancer costs. Approximately 10% of metastatic CRC (mCRC) patients have the BRAF V600E mutation, which is associated with a poorer prognosis than patients with BRAF wild-type mCRC.

BRAF inhibitors have shown clinical activity as single-agent therapies in BRAF V600E-mutant melanoma and non-small-cell lung cancer, but lack clinical efficacy in BRAF V600E-mutant mCRC. BEACON CRC (NCT02928224, hereafter referred to as BEACON) is the only Phase 3 randomised controlled trial (RCT) that has been conducted specifically in BRAF-mutant mCRC patients after prior systemic therapy. In BEACON, the combination treatment of the BRAF inhibitor encorafenib and the antiepidermal growth factor receptor monoclonal antibody cetuximab showed a statistically significant improvement in median overall survival (OS) (9.3 months) compared with cetuximab and chemotherapy (FOLFIRI (folinic acid, fluorouracil and irinotecan) or irinotecan) (5.9 months). These results led to the approval of encorafenib with cetuximab in BRAF V600E-mutant mCRC after prior systemic therapy in adults by the US Food and Drug Administration (April 2020) and the European Medicines Agency (June 2020). Both the National Comprehensive Cancer Network guidelines and the European Society of Medical Oncology pocket guideline recommend the combination of encorafenib with cetuximab in this patient population.

We developed a model to evaluate the cost-effectiveness of encorafenib with cetuximab compared with cetuximab with FOLFIRI or irinotecan, cetuximab alone, and bevacizumab with FOLFIRI in adult patients with BRAF V600E-mutant mCRC after prior systemic therapy, from the perspective of the French healthcare system.

**METHODS**

**Population**

The population considered by the cost-effectiveness model consisted of adult patients with mCRC with the BRAF V600E mutation after prior systemic therapy. The baseline characteristics of this population were those of the patient population in BEACON. This population is also aligned with the European marketing authorisation for encorafenib with cetuximab for mCRC and a French retrospective study (see online supplemental table S1).

**Interventions and comparators**

The model considered encorafenib with cetuximab (enco-cetux) as the intervention and three treatments as comparators (ie, cetuximab with FOLFIRI or irinotecan (cetux-FOLFIRI/iri), FOLFIRI alone (FOLFIRI), bevacizumab with FOLFIRI (beva-FOLFIRI)), as appropriate according to guidelines and French clinicians specialising in the treatment of mCRC. The clinical evidence for the comparators is extremely limited in this patient population, as prior to enco-cetux, no therapies were specifically indicated for BRAF-mutant patients with mCRC. Patients with this mutation have so far been treated as all comers or wild-type KRAS (Kirsten rat sarcoma viral oncogene homologue) patients, among whom BRAF-mutant patients are a subgroup (these two mutation types being mutually exclusive), and the treatment usage in clinical practice varies between countries.

The intervention (enco-cetux) and one of the comparator treatments (cetux-FOLFIRI/iri) were assessed in BEACON. For the remaining two comparator treatments (FOLFIRI and beva-FOLFIRI), a systematic literature review (SLR) identified seven peer-reviewed RCTs assessing BRAF-mutant patients in second-line treatment (see online supplemental table S2). Of these, one trial included FOLFIRI (Peeters et al) and one trial included beva-FOLFIRI (Shitara et al).

Peeters et al provided data from a BRAF-mutant subgroup that could be linked to BEACON via cetuximab with FOLFIRI and allowed an indirect treatment comparison (ITC) between enco-cetux and FOLFIRI to be conducted (see online supplemental figure S1), showing that enco-cetux was associated with a statistically significant lower hazard of death compared with FOLFIRI (HR: 0.39 (95% CI 0.19 to 0.81)) and disease progression (HR: 0.30 (95% CI 0.14 to 0.68)). This evaluation included panitumumab with FOLFIRI as the test treatment but not cetuximab with FOLFIRI, and so, for the comparison of enco-cetux to FOLFIRI in our analysis, we assumed equivalence between cetux-FOLFIRI/iri (from BEACON) and panitumumab with FOLFIRI (from Peeters et al).

Shitara et al included a subgroup of only five BRAF-mutant patients with mCRC treated with either beva-FOLFIRI or panitumumab with FOLFIRI as second-line treatment, which precluded its use in an ITC due to the small sample size, so the SLR was extended to include first-line treatment and wild-type KRAS patients. As a result, a further five trials (seven publications) were identified that compared cetuximab with FOLFIRI and beva-FOLFIRI, of which one trial reported significant results in favour of cetuximab with FOLFIRI with the other trials suggesting equivalence. Despite this treatment difference, a conservative approach was used in our base-case analysis and assumed equivalence between cetuximab with FOLFIRI and beva-FOLFIRI. A scenario analysis was conducted using the data from the trial reporting significant results in favour of cetuximab with FOLFIRI.

**Model construction**

**Perspective and model structure**

The model was developed in alignment with international health economic guidelines and best practices including the Modeling Good Research Practices and the National Institute for Health and Care Excellence (NICE) Decision Support Unit Technical Support Document 14 (DSU TSD 14) and was conducted from the perspective of the French healthcare system. Per French guidelines, model costs were estimated from a healthcare collective perspective (all person or institution affected,
including healthcare payer, private insurance and out-of-pocket costs in relation with healthcare).32

A partitioned survival model (PSM) was used to partition outcomes of OS, progression-free survival (PFS) and postprogression survival, using data from BEACON.3 Three limitations due to its fundamental assumption (that the survival functions are independent), this structure was deemed the most appropriate based on the type of data available to inform the model and the widely accepted suitability of PSM in oncology, according to NICE DSU TSD 19.33

Three mutually exclusive health states were defined: (1) progression-free (PF) state (the starting health state, defined as the time from the start of treatment to disease progression or death), (2) post-progression (PP) state (the time after first progression until death) and (3) death. Disease progression was defined as per the BEACON trial.3

Costs and utility weights for each health state were multiplied by the time spent alive for each health state to obtain overall outcomes (costs, life years (LYs), and quality-adjusted life years (QALYs)). The probability of patients residing in each health state for any given time point was calculated as follows.

1. PF: probability a patient had not yet progressed and was still alive, as calculated from the PFS curve.
2. PP: probability a patient was alive, as calculated from the OS curve)—probability a patient had not yet progressed and was still alive, as calculated from the PFS curve.
3. Death: 1—probability a patient was alive, as calculated from the OS curve).

**Time horizon and cycle length**

The model considered a lifetime horizon (until 0% of modelled patients remain alive, ie 30 years), as recommended for chronic diseases by economic guidelines,32 so that all expected incurred costs and effects were accounted for.

The cycle length was set at 1 month, which is sufficient to account for changes in health states or treatment strategies, and long enough not to impair computational efficiency. Moreover, because trial endpoints included in the model were based on the observation of patients with the event at the end of the month, a half-cycle correction was used to control for the uncertainty from the occurrence of events.

A discount rate of 2.5% was used for both costs and health outcomes, in accordance with French guidelines.32

**Outcomes and extrapolation of data**

The OS, PFS and time to treatment discontinuation (TTD) data were extrapolated beyond the BEACON trial duration to fulfill the lifetime horizon in the model. Survival extrapolation models were developed based on the NICE DSU TSD 14 recommendations.31

The final analysis of BEACON was performed using a cut-off date of August 2019 (median follow-up of 12.78 months (95% CI 12.19 to 14.13)).34 However, to limit the uncertainty around the long-term OS extrapolation in the economic analysis, OS data were extracted using an exploratory cut-off of May 2020 (median follow-up of 21.19 months (95% CI 19.42 to 22.51)), giving the following results, which are aligned with the results of the prespecified analysis of August 2019: stratified HR 0.63 (95% CI 0.51 to 0.78); median 9.40 months (95% CI 8.11 to 11.24) for enco-cetux and 5.88 months (5.09–7.16) for cetux-FOLFIRI/irI. Data were used until the last observed patients, despite the uncertainty associated with the end of the survival curve which was managed with external validation as described later in this section, since their exclusion would mean that longer term survival data would be ignored.31

Assessing OS data for modelling, an abrupt change in trajectory for the hazard rate at 2.8 months was identified for enco-cetux, probably due to the disease responding quickly to the treatment (see online supplemental figure S2). To account for this, a piecewise modelling approach was used to fit the parametric extrapolated curve from 2.8 months, providing a better fit than an extrapolation from the full data. Observed Kaplan-Meier data were used until 2.8 months. The statistical fit considered only the time period in which the parametric models are fitted to the observed data. For cetux-FOLFIRI/irI, no significant change in the hazard rate was identified, so the full data set from time 0 was used for parametric extrapolation. As survival extrapolation started at different time points for the two treatment arms, models were fitted independently. In order to apply the same distribution between the two arms of BEACON, as aligned with NICE technical guidelines,31 the Akaike and Bayesian information criteria (AIC and BIC, respectively) of both arms were compared; the log-conditional survival probabilities from real-world data in a large cohort of Nordic patients, which assessed BRAF-mutant mCRC35 (see online supplemental figure S3). A scenario sensitivity analysis was conducted applying the second-best fitting curve, that is, the generalised gamma.

For the comparison against FOLFIRI, the HR from the ITC was applied to the enco-cetux curve to generate the OS curve; for the comparison against beva-FOLFIRI, the OS curve of cetux-FOLFIRI/irI was used, based on the conservative assumption of equivalence between the two treatments. The HR of the only study associated with a statistically significant result25 was applied to the cetux-FOLFIRI/irI curve to generate the curve for the scenario analysis.

For PFS data, which were relatively mature at the predefined August 2019 data cut-off (76% and 67% of events in the treatment and control arms, respectively), and given that no parametric distribution fitted the data well, no extrapolation of the Kaplan-Meier data was conducted, which is a conservative approach. In the
same way as for OS, the HR and assumptions were used to compare to FOLFIRI and beva-FOLFIRI.

In BEACON, patients could have discontinued treatment before disease progression (eg, due to adverse events (AEs) or following an investigator or patient decision) or could have continued treatment after disease progression (eg, if there was an expected benefit). Thus, instead of assuming that treatment terminated with disease progression, TTD was analysed to better estimate treatment duration and to capture the most accurate costs associated with the primary treatments. Standard parametric distributions were fitted to the Kaplan-Meier data. According to the AIC/BIC criteria and visual inspection, the generalised gamma curve provided the best fit to both arms. Given that no information on the duration of treatment of FOLFIRI and beva-FOLFIRI were available, PFS was used as a proxy for these comparators. A scenario sensitivity analysis was conducted applying PFS for all treatment arms as a proxy of treatment duration.

Adverse events
The model included treatment-emergent AEs of grade 3 and above that occurred at an incidence of ≥2% in any comparator arm; data available from BEACON. The impact of less severe or common AEs on the model results was assessed to be negligible. The modelled rates of AEs were not extrapolated, since most patients in BEACON discontinued treatment during the study and were incorporated in the model as a one-time cost within the first treatment cycle. For comparators not assessed by BEACON and in the absence of such data for BRAF-mutant patients, the best available published data were used: AEs of grade 3 and above (with an incidence of ≥2%) from wild-type KRAS patients were used for FOLFIRI and beva-FOLFIRI. The AEs included are listed in online supplemental table S3.

Costs and resource use
The following costs were included:

- Costs of primary treatment (intervention and comparators), including drug costs, dispensing and administration costs.
- Costs of subsequent treatments, including drug costs, dispensing and administration costs.
- Resource use costs.
- Costs of treatment for AEs.

The treatments dosages were in line with their recommended usage in the patient population. The list prices of each treatment were included (see online supplemental table S4).

The treatments used and their proportion of usage after discontinuation of the primary treatments were based on BEACON data and clinical experience (see online supplemental table S5).

Resource use for BRAF-mutant patients with mCRC after prior systemic therapy in France was based on clinical expert opinions. Costs were extracted from the literature and from usual French national sources (see online supplemental table S6).

Relative dose intensity and molecule to treatment exposure ratio
The relative dose intensity (RDI) was applied to primary treatments to take into account dosage changes and temporary treatment discontinuations during the course of treatments. This was obtained from BEACON, or from assumptions for treatments not assessed by this trial. For FOLFIRI and beva-FOLFIRI, an identical RDI to cetux-FOLFIRI/iri (from BEACON) was assumed. To take into account the possibility of a patient discontinuing one molecule of a combination regimen, a ratio of molecule by treatment exposure was also included.

Quality of life inputs
Utility values were estimated from EQ-5D-5L data from BEACON, which represented the best available source of data. For FOLFIRI and beva-FOLFIRI, utility values of cetux-FOLFIRI/iri (from BEACON) were used. A
Scenario sensitivity analysis was conducted using the same utility value across all treatment arms.

Based on French tariffs, the mean (SD) utility values preprogression were 0.889 (0.154) (cetux-FOLFIRI/iri) and 0.883 (0.159) (both treatment arms in BEACON) for the scenario analysis; the postprogression value was 0.840 (0.211) in both arms. The preprogression utility took into account the effect of treatment-emergent AEs on quality of life, hence no disutility was applied; postprogression, the same treatment- and results were compared (see online supplemental table S7).

### Estimation of outcomes
The effectiveness outcomes of the model were expressed in terms of incremental LYs gained and incremental QALYs gained. The cost-effectiveness of enco-cetux was assessed by the incremental cost-effectiveness ratio (ICER), which provides a ratio of extra cost incurred per extra unit of health effect gained (LYs or QALYs). Because multiple interventions were assessed, the cost-effectiveness frontier was also generated (see online supplemental figure S4).

### Sensitivity analyses

#### Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was used to identify the parameters and assumptions with the greatest impact on the results. Upper and lower values of model inputs were included and varied in the model separately, and results were compared (see online supplemental table S7).

#### Scenario sensitivity analysis

Structural assumptions were tested through scenario sensitivity analyses, including the efficacy of beva-FOLFIRI, the modelling of OS, the modelling of treatment duration and the utility value preprogression (see online supplemental table S8).

### Statistical analysis

This economic analysis presents all results probabilistically. Results were produced with 10,000 Monte Carlo simulations, after assigning probability distributions to variables in the model with statistical uncertainty and repeatedly sampling values from these distributions to estimate results38 (see online supplemental table S9). Results are presented as the mean of the 10,000 computed simulations. This approach accounts for the uncertainty around the model parameters. Probabilities of being cost-effective were estimated from these data, based on a willingness-to-pay threshold of €90 000/QALY, corresponding to an average of 3x gross domestic product per capita (France), as recommended by the WHO.39 This threshold is relevant for the current analysis, that is, for a severe disease with high burden and mortality, and short

### Table 2 Costs per patient for encorafenib with cetuximab, cetuximab with FOLFIRI or irinotecan, FOLFIRI alone and bevacizumab with FOLFIRI

<table>
<thead>
<tr>
<th>Discounted cost (£)</th>
<th>Encorafenib with cetuximab</th>
<th>Cetuximab with FOLFIRI or irinotecan</th>
<th>FOLFIRI alone</th>
<th>Bevacizumab with FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary treatment cost</td>
<td>57 251 (48 481; 66 423)</td>
<td>15 150 (12 609; 16 964)</td>
<td>58 494 (47 444; 70 727)</td>
<td>13 800 (12 391; 15 368)</td>
</tr>
<tr>
<td>Routine management for primary treatment</td>
<td>12 082 (91 013; 15 684)</td>
<td>5 407 (4 213; 6 829)</td>
<td>4 740 (3 693; 5 987)</td>
<td>6 022 (4 692; 7 606)</td>
</tr>
<tr>
<td>Postdiscontinuation therapy cost</td>
<td>20 799 (13 780; 29 544)</td>
<td>16 678 (12 132; 22 200)</td>
<td>7 771 (6 108; 9 768)</td>
<td>15 823 (11 774; 20 653)</td>
</tr>
<tr>
<td>Best supportive care cost</td>
<td>8 838 (5994; 12 970)</td>
<td>4 757 (3 258; 6 687)</td>
<td>2 384 (1 745; 3 168)</td>
<td>4 562 (3 168; 6 344)</td>
</tr>
<tr>
<td>Adverse event cost</td>
<td>25 71 (2098; 3109)</td>
<td>5 602 (4 548; 6 745)</td>
<td>3 106 (2 514; 3 750)</td>
<td>5 464 (4 448; 6 608)</td>
</tr>
<tr>
<td>Total cost</td>
<td>101 541 (87 702; 116 895)</td>
<td>47 594 (41 123; 55 112)</td>
<td>23 851 (20 811; 27 368)</td>
<td>45 671 (39 542; 52 699)</td>
</tr>
<tr>
<td>Incremental cost vs encorafenib with cetuximab</td>
<td>–</td>
<td>53 947 (39 657; 68 892) p&lt;0.001</td>
<td>77 690 (65 583; 90 909) p&lt;0.001</td>
<td>55 870 (42 137; 70 582) p&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Undiscounted cost (£)</th>
<th>Encorafenib with cetuximab</th>
<th>Cetuximab with FOLFIRI or irinotecan</th>
<th>FOLFIRI alone</th>
<th>Bevacizumab with FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary treatment cost</td>
<td>57 305 (48 216; 66 847)</td>
<td>15 215 (12 648; 17 042)</td>
<td>58 494 (47 322; 70 095)</td>
<td>13 809 (12 384; 15 428)</td>
</tr>
<tr>
<td>Routine management for primary treatment</td>
<td>12 116 (9157; 15 894)</td>
<td>5 436 (4 230; 6 389)</td>
<td>4 745 (3 691; 6 014)</td>
<td>6 032 (4 693; 7 646)</td>
</tr>
<tr>
<td>Postdiscontinuation therapy cost</td>
<td>24 135 (15 571; 34 749)</td>
<td>17 628 (12 660; 23 844)</td>
<td>7 867 (6 185; 9 836)</td>
<td>16 811 (12 327; 22 200)</td>
</tr>
<tr>
<td>Best supportive care cost</td>
<td>10 257 (6450; 15 165)</td>
<td>5 019 (3 444; 7 100)</td>
<td>2 407 (1 761; 3 210)</td>
<td>4 826 (3 346; 6 724)</td>
</tr>
<tr>
<td>Adverse event cost</td>
<td>25 71 (2098; 3109)</td>
<td>5 602 (4 548; 6 745)</td>
<td>3 106 (2 514; 3 750)</td>
<td>5 464 (4 448; 6 608)</td>
</tr>
<tr>
<td>Total cost</td>
<td>106 384 (90 852; 124 012)</td>
<td>48 900 (41 934; 57 010)</td>
<td>23 974 (20 963; 27 396)</td>
<td>46 942 (40 471; 54 690)</td>
</tr>
<tr>
<td>Incremental cost vs encorafenib with cetuximab</td>
<td>–</td>
<td>57 484 (41 627; 74 596) p&lt;0.001</td>
<td>82 410 (68 494; 97 782) p&lt;0.001</td>
<td>59 442 (43 888; 76 556) p&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean (95% CI) cost. FOLFIRI, folinic acid, fluorouracil and irinotecan.
survival of 4.7 months, where innovative options with clinically relevant additional survival benefits versus standard of care are needed. To estimate CIs, the 2.5th and 97.5th centiles from the 10,000 simulations were taken. To estimate a two-sided p value for the incremental costs, we took the proportion of the 10,000 simulations where costs were lower for enco-cetux than the comparator and then multiplied by 2. The same approach was applied to incremental LYSs and QALYs.

Patient and public involvement
None.

RESULTS
Life years and QALYs gained
Based on the full study population of patients with mCRC with the BRAF V600E mutation, over a lifetime horizon the use of enco-cetux resulted in a mean of 21.9 months of life (95% CI 17.5 to 26.9 months) compared with 11.1 months (95% CI 9.2 to 13.3 months) for cetux-FOLFIRI/iri and for beva-FOLFIRI (ie, an increased life expectancy of 10.8 months (95% CI 5.7 to 16.2 months), p<0.001) and 6.4 months (95% CI 5.7 to 7.3 months) for FOLFIRI (ie, an increased life expectancy of 15.5 months (95% CI 11.6 to 19.9 months), p<0.001). The time spent progression-free approximately doubled for enco-cetux (6.2 months) compared with cetux-FOLFIRI/iri and beva-FOLFIRI (3.3 months) and was almost 2.5 times higher than for FOLFIRI (2.6 months). The QALY gain of enco-cetux compared with cetux-FOLFIRI/iri and beva-FOLFIRI was 0.8 (95% CI 0.4 to 1.1, p<0.001) and compared with FOLFIRI was 1.1 (95% CI 0.8 to 1.4, p<0.001) (table 1).

Costs
The total costs per patient were €101,541 (95% CI €87702–€116,895) for enco-cetux, €47,594 (95% CI €41,123–€55,112) for cetux-FOLFIRI/iri, €23,851 (95% CI €20,811–€27,368) for FOLFIRI and €45,671 (95% CI €39,542–€52,699) for beva-FOLFIRI (table 2). The total incremental cost compared with enco-cetux was €53,947 (95% CI €39,657–€68,892, p<0.001) for cetux-FOLFIRI/iri, €77,690 (95% CI €65,583–€90,909, p<0.001) for FOLFIRI and €55,870 (95% CI €42,137–€70,582, p<0.001) for beva-FOLFIRI (table 2). The increased cost for enco-cetux was mainly due to higher primary treatment costs and routine management costs, partly driven by increased life expectancy and, therefore, a longer treatment duration. The costs related to AEs were lower for enco-cetux (€2571, 95% CI €2098–€3109) than cetux-FOLFIRI/iri (€5602, 95% CI €4548–€6745), FOLFIRI (€3106, 95% CI €2514–€3750) and beva-FOLFIRI (€5464, 95% CI €4408–€6608).

Incremental cost-effectiveness ratio
The estimated ICERS were €69,823/QALY, €70,421/QALY and €72,336/QALY for enco-cetux versus cetux-FOLFIRI/iri, FOLFIRI and beva-FOLFIRI, respectively (table 3).

The Monte Carlo simulations for ICER versus cetux-FOLFIRI/iri are shown in figure 1. The cost-effectiveness acceptability curve showed 89.8%, 98.2% and 86.4% probability that the ICER falls below the commonly accepted willingness to pay threshold of €90,000/QALY versus cetux-FOLFIRI/iri, FOLFIRI and beva-FOLFIRI, respectively (see online supplemental figure S3).

Three interventions form the cost-effectiveness frontier; the ICER of beva-FOLFIRI versus FOLFIRI was €64,176/QALY, and the ICER of enco-cetux versus beva-FOLFIRI was €72,558/QALY (see online supplemental figure S4).

Deterministic sensitivity analysis
The parameters with the most impact on ICER were the ratio of molecule by treatment exposure for encorafenib and the unit cost of the administration vial (figure 2). The highest ICER (€71,649/QALY) increased the base case ICER versus cetux-FOLFIRI/iri (€69,823/QALY) by 3%, indicating a low parametric uncertainty.

Scenario sensitivity analysis
Scenario sensitivity analyses are presented in online supplemental table S8. Applying a different parametric distribution for OS resulted in higher ICERS compared with the base-case analysis and the largest variations. It should, however, be emphasised that the best extrapolation fit externally validated with long-term observational data was used for the base case. Applying PFS as a proxy of treatment duration and HR to estimate the efficacy of beva-FOLFIRI resulted in lower ICERS compared with the base-case analysis, whereas applying the same utility value for all treatment arms before progression had negligible impact on ICERS.

DISCUSSION
The primary analysis showed that enco-cetux treatment resulted in an ICER of €69,823/QALY compared with cetux-FOLFIRI/iri. The analyses versus FOLFIRI and beva-FOLFIRI showed similar ICERS of €70,421/QALY.

Table 3 Incremental cost-effectiveness ratio analysis for encorafenib with cetuximab compared with cetuximab with FOLFIRI or irinotecan, FOLFIRI alone and FOLFIRI with bevacizumab

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Total cost (discounted) (£)</th>
<th>QALY</th>
<th>ICER (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encorafenib with cetuximab</td>
<td>101,541</td>
<td>1.56</td>
<td>–</td>
</tr>
<tr>
<td>Cetuximab with FOLFIRI or irinotecan</td>
<td>47,594</td>
<td>0.79</td>
<td>69,823</td>
</tr>
<tr>
<td>FOLFIRI alone</td>
<td>23,851</td>
<td>0.45</td>
<td>70,421</td>
</tr>
<tr>
<td>Bevacizumab with FOLFIRI</td>
<td>45,671</td>
<td>0.79</td>
<td>72,336</td>
</tr>
<tr>
<td>FOLFIRI, folic acid, fluorouracil and irinotecan; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.</td>
<td></td>
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</table>
and €72 336/QALY (€61 980/QALY using HR from the only study showing statistically significant results), respectively. There was 89.8%, 98.2% and 86.4% (99.6% in the scenario analysis) probability that encorafenib was considered cost-effective compared with cetuximab-FOLFIRI/ir, FOLFIRI and bevacizumab-FOLFIRI, respectively, at the commonly accepted willingness to pay threshold of €90 000/QALY. These results use publicly available drug treatment costs as the driving costs of the analysis and do not consider potential confidential pricing agreements.

Our findings contrast with three previous cost-effectiveness analyses of encorafenib for the treatment of BRAF-mutant mCRC. The first one, conducted in the US setting, gave an ICER of $523 374/QALY and concluded that the treatment...

Figure 1 Scatterplot of incremental costs and QALYs for encorafenib with cetuximab compared with cetuximab with FOLFIRI or irinotecan. FOLFIRI, folinic acid, fluorouracil and irinotecan; Incr, increment; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 2 Tornado analysis for the incremental cost-effectiveness ratio (ICER) for encorafenib with cetuximab compared with cetuximab with FOLFIRI or irinotecan. AE, adverse event; BSC, best supportive care; Cetux, cetuximab; Enco, encorafenib; FOLFIRI, folinic acid, fluorouracil and irinotecan; Ir, irinotecan; QALY, quality-adjusted life year; RDI, relative dose intensity; tx, treatment.
was not cost-effective. However, this previous analysis used a Markov model structure that focused mainly on the costs of transitioning through treatment lines and disregarded the benefit of delaying disease progression, using the same utility score preprogression and postprogression for all interventions. This approach underestimates the QALY gain offered by an intervention extending the time spent without progression, associated with a better quality of life. Our analysis used a PSM based on the Kaplan-Meier curves from BEACON and derived different utility scores preprogression and postprogression from this trial. The partitioned survival approach has the advantage of being able to use the overall trial PFS and OS data directly without separate estimation of transition probabilities as with a Markov model. Moreover, the previous analysis estimated OS indirectly by varying the transition probabilities incrementally from best supportive care to death, with a calibration exercise to reach the median OS from BEACON. This approach appears less reliable to estimate the clinical outcomes compared with our analysis, which relies directly on the Kaplan-Meier curves. The previous analysis resulted in a QALY gain of 0.15 for enco-cetux versus cetux-FOLFIRI/iri, compared with 0.80 from our analysis. Using BEACON Kaplan-Meier curves while capturing the benefit of delaying disease progression clearly better reflect treatment effect.

Another published US cost-effectiveness analysis of enco-cetux for the treatment of BRAF-mutant mCRC resulted in an ICER of $435 450/QALY, with OS modelled using the Kaplan-Meier curves with a Weibull distribution from BEACON and a data cut-off of February 2019. This has possibly underestimated the clinical value of the intervention compared with our analysis, which used more mature BEACON data (May 2020 cut-off) with a piecewise approach validated by the evidence review group from NICE, accurately and precisely adapting to BEACON data with a log-logistic distribution as the best statistical fit. Our modelling approach was also validated against external data from a Nordic cohort providing long-term survival. This second previous cost-effectiveness analysis resulted in a QALY gain of 0.14 for enco-cetux versus cetux-FOLFIRI/iri, compared with 0.80 for our analysis.

A third previous cost-effectiveness analysis was recently published from an Italian perspective and resulted in an ICER of €175 900/month of OS gain, with the difference in treatment effect being estimated using median OS. This approach is not supported by economic evaluation guidelines; NICE prescribes the use of the mean rather than the median effect, and modelling OS by using/extrapolating Kaplan-Meier data represents best practice. Moreover, the analysis ignored the benefits of delaying disease progression, improving quality of life and decreasing AE costs. This approach appears to underestimate the QALY gain and overestimate the costs associated with the intervention.

Overall, the analytical approaches used by the three previous analyses do not appear to conform to good modelling practices and may not accurately represent the benefits or cost-effectiveness of enco-cetux. As such, we challenge their validity and strongly believe their results and conclusions should be viewed with significant caution.

One potential limitation of our analysis is the generalisability of BEACON to all patients who will receive the treatment in real life in the French setting, considering that this is a multinational trial with criteria excluding some patients who could receive the treatment in real life, and that the comparator was not representing all options available and used in clinical practice. However, BEACON was the first RCT specifically designed for assessing BRAF-mutant mCRC patients and enco-cetux the first intervention specifically indicated for this population. Moreover, the generalisability of BEACON to the French perspective was concluded as well acceptable when patient characteristics were compared with a French cohort assessing the population of interest (see online supplemental table S1).

Another limitation relates to the small amount of data that were available in BRAF-mutant patients, which meant that assumptions were needed for the comparator treatments that were not included in BEACON. For the comparison versus beva-FOLFIRI, the generalisation of evidence in wild-type KRAS patients and in first line of treatment to BRAF-mutant patients in second and third lines of treatment was needed. For the comparison versus FOLFIRI, cetuximab and panitumumab were assumed to be equivalent, allowing the ITC. Also, the population of BRAF-mutant patients in the FOLFIRI trial was approximately 10-fold smaller than in BEACON (N=44 vs N=441), reducing the robustness of the comparison. Furthermore, the FOLFIRI trial baseline characteristics were not available for the BRAF-mutant population. Although it was not possible to quantify the effect of these limitations, the assumptions that we used were made through expert consensus and systematic review of the available literature, and the ITC of enco-cetux versus FOLFIRI was validated by the evidence review group from NICE. In the future, if more data become available for BRAF-mutant patients, especially for FOLFIRI and beva-FOLFIRI, they could be incorporated into the model.

In conclusion, this analysis showed enco-cetux to be a cost-effective treatment in patients with mCRC with the BRAF V600E mutation.

Author affiliations
1Department of Public Health, Aix-Marseille University, Marseille, France
2Pierre Fabre Laboratories, Paris, France
3Pierre Fabre Laboratories, Reading, UK
4Mtech Access, Bicester, UK
5Creativ Ceutical, Paris, France
6Medical Oncology Department, Gustave Roussy, Université Paris-Saclay, Villejuif, France
7Medical Oncology Department, Institut du Cancer de Montpellier, Montpellier, France

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**ORCID iDs**

Jean-Baptiste Trouiller http://orcid.org/0000-0002-1055-9858

David Malka http://orcid.org/0000-0002-7664-0130

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