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

Lead team presentation

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Chair: Amanda Adler
ERG: Warwick Evidence
Technical team: Jessica Cronshaw, Lorna Dunning, Nicole Elliott
Company: Pierre Fabre
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Key issues

1. Treatment pathway:
   - What is the appropriate position in the treatment pathway?
     • 2\textsuperscript{nd} and/or 3\textsuperscript{rd} line?
   - What are the relevant comparators at 2\textsuperscript{nd} line?

2. In absence of a direct comparison, are the results valid from the:
   • indirect treatment comparison?
   • naïve comparison?

3. What are the most appropriate models for extrapolating:
   - Overall survival (OS)
   - Progression-free survival (PFS)

4. How should time to treatment discontinuation (TTD) be modelled?

5. Are the costs included appropriately?

6. Does encorafenib + cetuximab meet NICE’s end of life criteria?

NICE
BRAF V600E mutation-positive metastatic colorectal cancer

- Metastatic colorectal cancer: malignant tumour of the large intestine (colon and rectum), that has spread beyond the large intestine and nearby lymph nodes.
- 10% of people with colorectal cancer have tumours with the BRAF V600E mutation
- Metastatic colorectal cancer with BRAF mutation, associated with poorer prognosis and greater risk of disease recurrence than ‘wild-type’ (‘normal’ non-mutated)
- NICE clinical guideline 151 recommends testing for BRAF V600E mutations in all people with metastatic colorectal cancer suitable for systemic anti-cancer treatment
- Aim of treatment for metastatic colorectal cancer is to prolong survival and improve quality of life
- Currently no treatments available specifically for tumours with BRAF V600E mutations
# Encorafenib (BRAFTOVI, Pierre Fabre)

<table>
<thead>
<tr>
<th>Marketing authorisation</th>
<th>Adult patients with metastatic colorectal cancer with BRAF V600E mutation, who have had prior systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td><strong>Encorafenib</strong>: blocks MAPK# cell signalling pathway in BRAF V600E mutation-positive tumours <strong>In combination with cetuximab</strong>: prevents activation of feedback loop (EGRF) that BRAF inhibition alone would activate</td>
</tr>
<tr>
<td>Additional tests</td>
<td>Must confirm BRAF V600E mutation with a validated test</td>
</tr>
<tr>
<td>Administration and dose</td>
<td><strong>Encorafenib</strong>: oral. 300 mg (four 75 mg capsules) once daily. Continue until patient no longer benefits or until development of unacceptable toxicity <strong>Cetuximab</strong>: intravenous. Initial dose 400 mg/m² body surface area, all subsequent doses 250 mg/m² weekly*</td>
</tr>
<tr>
<td>Cost</td>
<td><strong>Encorafenib</strong>: List price - £1,400 per pack of 42 x 75 mg capsules, £622.22 per pack of 28 x 50 mg capsules <strong>Cetuximab</strong>: List price - £890.50 per 500 mg/100 mL† Commercial arrangements in place for encorafenib and cetuximab, making them available to the NHS with a discount. Cetuximab made by Merck.</td>
</tr>
</tbody>
</table>

\# MAPK = mitogen-activated protein kinase  
†National Cancer Drugs Fund list*: recommends cetuximab is given once every 2 weeks at a dose of 500mg/m²
Professional organisation perspective

Submission from Royal College of Physicians

- BRAF mutant colorectal cancer is a very rare sub-type of colorectal cancer.
- Very little shift in median survival for BRAF mutant cancer, despite advances in RAS wild type (‘normal’ non-mutated) colorectal cancer.
- FOLFIRI or alternatively trifluridine-tipiracil are currently used in clinical practice for BRAF mutant colorectal cancer.
- Encorafenib + cetuximab would be used in 2nd or 3rd line.
- No significant difference in adverse events expected compared with current treatments.
- Encorafenib + cetuximab represents a ‘step-change’ in treatment. It is the only treatment to date that demonstrates both a clinically meaningful and statistically significant difference in terms of overall survival in this patient population in a phase 3 trial.
Patient and carer perspectives

Unmet need

• Little movement in the drugs used for many years; survival has hardly improved in the last 5 years
• Mental and physical challenges from poor prognosis

Novel treatment options required

• Current treatment is harsh, 21 cycles and 2 years later I still have neuropathic damage

Encorafenib + cetuximab

• Treatment* gave me life, and response was quick
• Suggest using sooner rather than last line
• Adverse effects are manageable with education, but more knowledge on best ways to manage them must be obtained whilst in use.
  – “Change of Bowel Habits, Eye changes, Skin rashes and Tiredness are for me the key side effects.”

NICE *Patient expert received triplet therapy which is not included in company submission
## The decision problem

<table>
<thead>
<tr>
<th>Population</th>
<th>Final scope issued by NICE</th>
<th>Company submission deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>People with previously treated BRAF V600E mutation-positive metastatic colorectal cancer</td>
<td>As in scope: company present evidence for people who received 1 or 2 prior therapies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Company submission deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Encorafenib + cetuximab</td>
<td></td>
</tr>
<tr>
<td>2. Encorafenib + cetuximab and binimetinib</td>
<td></td>
</tr>
<tr>
<td><strong>Company:</strong> Marketing authorisation for encorafenib + cetuximab</td>
<td></td>
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<tr>
<td>Triple therapy not relevant</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparators</th>
<th>Company submission deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Folinic acid plus fluorouracil plus irinotecan (FOLFIRI)</td>
<td></td>
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<tr>
<td>2. Trifluridine-tipiracil*</td>
<td></td>
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<tr>
<td>3. Irinotecan</td>
<td></td>
</tr>
<tr>
<td>4. Best supportive care</td>
<td></td>
</tr>
<tr>
<td><strong>Company exclude irinotecan</strong> because low use in practice based on clinical expert opinion and market survey</td>
<td></td>
</tr>
<tr>
<td><strong>Company exclude best supportive care</strong> because encorafenib + cetuximab would be used earlier in the treatment pathway, when active treatment options are still available</td>
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</tbody>
</table>

*after treatment with fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies or where these are not tolerated or unsuitable
Encorafenib + cetuximab: place in the treatment pathway

Marketing authorisation: Adult patients with metastatic colorectal cancer with BRAF V600E mutation, who have had prior systemic therapy

What is the committee’s view on the positioning in the treatment pathway - are both 2nd and 3rd line positionings acceptable? What are the potential comparators at each line?

Bowel cancer UK: encorafenib + cetuximab would be used 2nd line most frequently. 3rd line appropriate in patients who have progressed to 3rd line chemotherapy and have a performance status of 0-1
Encorafenib + cetuximab: appropriate comparators – 2\textsuperscript{nd} line

\textit{FOLFIRI assumed to be a comparator}

\textbf{Irinotecan}

\textbf{Company:} Systemic Anti-Cancer Therapy (SACT) data show 1.8% receive irinotecan 2nd line

\textbf{Bowel Cancer UK:} Irinotecan an established 2\textsuperscript{nd} line treatment, but used less than FOLFIRI

\textbf{Clinical experts submission to NICE:} Single agent irinotecan associated with many toxicities and FOLFIRI now preferred 2\textsuperscript{nd} line therapy

\textbf{Trifluridine-tipiracil}

\textbf{TA405:} In clinical practice, trifluridine–tipiracil offered at 3\textsuperscript{rd} line when there are no further treatment options

\textbf{Clinical experts submission to NICE:} UK pathway follows 1\textsuperscript{st} line FOLFOXIRI -> 2\textsuperscript{nd} line trifluridine-tipiracil or 1\textsuperscript{st} line FOLFOX/CAPOX ->2\textsuperscript{nd} line FOLFIRI ->3\textsuperscript{rd} line trifluridine-tipiracil

\textbf{Company:} trifluridine–tipiracil used either at 2\textsuperscript{nd}-line if all options are given in one regimen or at 3\textsuperscript{rd}-line if given sequentially (e.g. FOLFOX 1\textsuperscript{st}-line and FOLFIRI at 2\textsuperscript{nd}-line).

\textbf{ERG:} FOLFOXIRI 1\textsuperscript{st} line (2\textsuperscript{nd} line trifluridine-tipiracil) currently applies to a minority of patients, potential to increase if encorafenib + cetuximab approved at 2\textsuperscript{nd} line against trifluridine–tipiracil

\begin{itemize}
  \item Does everyone agree that single agent irinotecan is an inappropriate comparator?
  \item Is trifluridine-tipiracil an appropriate comparator after 1 prior therapy?
\end{itemize}
Appropriate comparators at 3\textsuperscript{rd} line

Company disregards best supportive care

1\textsuperscript{st} line

2\textsuperscript{nd} line

Encorafenib + cetuximab

3\textsuperscript{rd} line

Encorafenib + cetuximab

FOLFOX

FOLFOXIRI

FOLFIRI

Trifluridine-tipiracil TA405

Irinotecan

What are the comparators at 3\textsuperscript{rd} line?
Clinical effectiveness

No head to head trials for encorafenib + cetuximab with relevant comparators
Encorafenib + cetuximab
VS
FOLFIRI

Main trial has blended comparator not used in NHS practice
Indirect treatment comparison has no common link
Encorafenib + cetuximab vs FOLFIRI: BEACON CRC trial

Comparator in key trial does not reflect UK clinical practice

Population: BRAF V600E-mutant metastatic colorectal cancer, progressed after 1 or 2 prior regimens

Global multicentre, randomised, open-label, active controlled phase 3 study (n=665)

Safety lead in (n=37)

Intervention arm

Encorafenib + binimetinib + cetuximab* (n=224)

Intervention arm

Encorafenib + cetuximab* (n=220)

Control arm

Investigator’s choice of chemotherapy (FOLFIRI or irinotecan) plus cetuximab* (n=221)

*NICE guidance restricts the use of cetuximab to first-line therapy in England – trial does not represent clinical practice

Triple therapy not included in company submission

NICE
Encorafenib + cetuximab vs FOLFIRI: BEACON CRC results

Trial doesn’t address decision problem. Longer survival for encorafenib + cetuximab vs investigators’ choice (FOLFIRI or irinotecan) + cetuximab

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Encorafenib + cetuximab</th>
<th>(FOLFIRI or irinotecan) + cetuximab</th>
<th>Difference between the study groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, median no. months (95% CI)</td>
<td>9.30 (8.05-11.30)</td>
<td>5.88 (5.09-7.10)</td>
<td>HR=0.61 (0.48-0.77), p&lt;0.0001</td>
</tr>
<tr>
<td>PFS, median no. months (95% CI)</td>
<td>4.27 (4.07-5.45)</td>
<td>1.54 (1.48-1.91)</td>
<td>HR=0.44 (0.35-0.55), p&lt;0.0001</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>19.5 (14.5-25.4)</td>
<td>1.8 (0.5-4.6)</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Does Committee consider encorafenib + cetuximab more effective than FOLFIRI + cetuximab?
# Encorafenib + cetuximab vs FOLFIRI: additional clinical trial evidence. Indirect treatment comparison

*No head to head trials for encorafenib + cetuximab with relevant comparators*

Company identified 1 randomised controlled trial (Peeters et al. 2010/2015) for indirect treatment comparison (ITC) of encorafenib + cetuximab vs FOLFIRI

<table>
<thead>
<tr>
<th>Study title</th>
<th>BEACON CRC</th>
<th>Peeters et al. 2010/2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>RCT phase 3</td>
<td>RCT phase 3</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>BRAF V600E-mutant metastatic colorectal cancer ≤2 prior therapies Encorafenib + cetuximab</td>
<td>Metastatic colorectal cancer, 1 prior chemotherapy Subpopulation BRAF-mutant FOLFIRI + panitumumab</td>
</tr>
<tr>
<td><strong>Intervention(s)</strong></td>
<td>Encorafenib + cetuximab</td>
<td>FOLFIRI</td>
</tr>
<tr>
<td><strong>Comparator(s)</strong></td>
<td>Investigators choice (FOLFIRI or Irinotecan) + cetuximab</td>
<td>FOLFIRI</td>
</tr>
<tr>
<td><strong>1° outcomes</strong></td>
<td>Outcomes for triple arm therapy</td>
<td>Progression-free survival and overall survival</td>
</tr>
<tr>
<td><strong>2° endpoints</strong></td>
<td>Overall survival, overall response rate, progression free survival</td>
<td>Overall response rate</td>
</tr>
</tbody>
</table>

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; FOLFIRI, folinic acid plus 5-fluorouracil plus irinotecan. RCT Randomised controlled trial
Encorafenib + cetuximab vs FOLFIRI:
Company’s indirect treatment comparison

*No common comparator – not possible to connect network*

- No common comparators between BEACON CRC and Peeters et al
- So, company assumes equivalence between comparators
  1. FOLFIRI and irinotecan equally effective
  2. Cetuximab and panitumumab equally effective

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**BEACON**

```
Encorafenib + cetuximab
```

**FOLFIRI**

```
FOLFIRI + cetuximab
```

**Irinotecan**

```
Irinotecan + cetuximab
```

**FOLFIRI + panitumumab**

**FOLFIRI**

---

Within trial comparison

Grouping of node based on company assumptions and explored in company’s ITC.
Encorafenib + cetuximab vs FOLFIRI:
Company’s Indirect treatment comparison – another visual
Company assumes equivalence between comparators in trials for ITC

1 FOLFIRI and irinotecan have equivalent clinical effectiveness
   - Assumption from 2 clinical trials (not BRAF mutant population)

2 Cetuximab and panitumumab have equivalent clinical effectiveness
   - Equivalence assumed based on class effect, both EGRF inhibitors
   - Supported by NICE clinical experts and committee opinion NICE TA439
Encorafenib + cetuximab vs FOLFIRI: 
2 assumptions of the indirect treatment comparison

1. **Company assumes FOLFIRI and irinotecan equally effective**

   **ERG:** treatments in control arm not randomised
   company data suggest big differences between FOLFIRI + cetuximab vs irinotecan + cetuximab

   **Company:** Overall and progression free survival curves split between control arm treatments are broadly aligned

   **Clinical experts:** limited data but efficacy of FOLFIRI and irinotecan equal for wildtype and BRAF-mutant populations

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What’s the committee’s views on the assumption of equivalence for FOLFIRI and irinotecan? If equivalent, why aren’t they used equally in NHS?
Encorafenib + cetuximab vs FOLFIRI: 2 assumptions of the indirect treatment comparison

2. Cetuximab and panitumumab equally effective
• Company assumes class effect applies as both are EGFR inhibitors
• Company’s clinical experts support this
• Committee conclusion in NICE TA439 cetuximab and panitumumab for previously untreated metastatic colorectal cancer, ‘cetuximab and panitumumab were likely to have similar effectiveness in treating RAS wild-type metastatic colorectal cancer’

What’s the committee’s views on the assumption of equivalence for cetuximab and panitumumab?
Encorafenib + cetuximab vs FOLFIRI: benefit of cetuximab without encorafenib

Limited evidence on clinical effectiveness of cetuximab without encorafenib for BRAF V600E

Company

- Need to remove benefit of cetuximab in control arm to estimate relative efficacy of encorafenib + cetuximab vs FOLFIRI.
- Point estimates from 2 published meta-analyses (Pietrantonio 2015; Rowland 2015) favour EGFR inhibitors for progression-free survival and overall survival vs chemotherapy or best supportive care alone
  - but small sample size, wide confidence intervals, not statistically significant

Clinical experts:

- Cetuximab is an effective treatment for BRAF V600E but less than the wild type.

ERG:

Prefer use of data direct from BEACON CRC to estimate efficacy of encorafenib + cetuximab vs FOLFIRI

- Is cetuximab in combination with FOLFIRI or irinotecan, likely to provide additional clinical benefit for people with BRAF V600E mutations?
Encorafenib + cetuximab vs FOLFIRI results indirect treatment comparison

**BEACON CRC and ITC shows encorafenib + cetuximab improves overall survival and progression free survival compared with FOLFIRI**

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall survival (hazard ratio)</th>
<th>Progression free survival (hazard ratio)</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEACON CRC trial</td>
<td>Encorafenib + cetuximab vs. (FOLFIRI or irinotecan) plus cetuximab</td>
<td>0.61 (0.48, 0.77) 0.44 (0.35, 0.55)</td>
<td>Direct</td>
</tr>
<tr>
<td>Peeters et al. 2010/2015</td>
<td>FOLFIRI + panitumumab vs. FOLFIRI</td>
<td>0.64 (0.32, 1.28) 0.69 (0.32, 1.49)</td>
<td>Direct</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BEACON CRC trial Peeters et al. 2010/2015</td>
<td>Encorafenib + cetuximab vs. FOLFIRI</td>
<td>0.39 (0.19, 0.81) 0.30 (0.14, 0.68)</td>
<td>Indirect</td>
</tr>
</tbody>
</table>

ERG use OS and PFS directly

- **What is the committee’s view on the source of efficacy data for encorafenib + cetuximab vs FOLFIRI?**
- **Are results direct from BEACON CRC or from the ITC more appropriate?**
Encorafenib + cetuximab
vs
trifluridine-tipiracil

No direct trial data
Encorafenib + cetuximab vs trifluridine-tipiracil - additional trial evidence

Indirect treatment comparison not possible - no data for BRAF-mutant cancer

- Company naively compared encorafenib + cetuximab using data from BEACON with data on trifluridine-tipiracil from RECOURSE.
- RECOURSE not done in BRAF mutant.

<table>
<thead>
<tr>
<th>Title</th>
<th>BEACON CRC</th>
<th>RECOURSE (Mayer 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>RCT phase 3</td>
<td>RCT phase 3</td>
</tr>
<tr>
<td>Population</td>
<td>BRAF V600E-mutant metastatic colorectal cancer ≤2 prior therapies</td>
<td>Metastatic colorectal cancer refractory or intolerant to standard therapies &gt;60% had ≥4 prior therapies</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Encorafenib + cetuximab</td>
<td>Trifluridine-tipiracil</td>
</tr>
<tr>
<td>Comparator(s)</td>
<td>Investigators choice (FOLFIRI or Irinotecan) + cetuximab</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>1° outcomes</td>
<td>Triple arm therapy outcomes only</td>
<td>Overall survival</td>
</tr>
<tr>
<td>2° endpoints</td>
<td>Overall survival, overall response rate, progression free survival</td>
<td>Performance status, progression free survival</td>
</tr>
</tbody>
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Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine-protein kinase B-Raf; FOLFIRI, folinic acid plus 5-fluorouracil plus irinotecan. RCT randomised controlled trial.
Encorafenib + cetuximab vs trifluridine-tipiracil: company’s naïve comparison

*Populations differ between 2 sources: BRAF mutant vs BRAF wild-type*

Survival from RE COURSE trial and BEACON trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Overall survival</th>
<th>Progression Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE COURSE</td>
<td>Trifluridine-tipiracil</td>
<td>7.1 (6.5, 7.8)</td>
<td>2.0 (1.9, 2.1)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>5.3 (4.6, 6.0)</td>
<td>1.7 (1.7, 1.8)</td>
</tr>
<tr>
<td>BEACON</td>
<td>Encorafenib + cetuximab</td>
<td>9.3 (8.1, 11.3)</td>
<td>4.3 (4.1, 5.5)</td>
</tr>
<tr>
<td></td>
<td>FOLFIRI / Irinotecan + cetuximab</td>
<td>5.9 (5.1, 7.1)</td>
<td>1.5 (1.5, 1.9)</td>
</tr>
</tbody>
</table>

**Company:** adjusts for difference in survival for BRAF-mutant vs BRAF wild-type populations using hazard ratios from the Peeters 2010/15 trial

- acknowledge the uncertainty of approach, but highlight paucity of data available

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BRAF V600E versus BRAF wild-type hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>4.0 (2.8, 5.6)</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>3.6 (2.5, 5.0)</td>
</tr>
</tbody>
</table>

Do the population differs in ways other than histology? Is this approach valid?
### Enocafenib + cetuximab vs trifluridine-tipiracil:

**Difference in survival BRAF V600E mutant vs wild type**

*Company* presented a meta-analysis (Safaee Ardekani et al. 2012) with an alternative estimate to adjust for difference in survival between BRAF and wild-type. Scenario uses HR= 2.24

<table>
<thead>
<tr>
<th>Source</th>
<th>Wildtype vs BRAF V600E adjustment for trifluridine tipiracil</th>
<th>MRC FOCUS (ERG alternative from meta analysis)</th>
<th>BEACON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peeters et al 2015</td>
<td>FOLFIRI + panitumumab vs FOLFIRI</td>
<td>Meta-analysis - 26 trials</td>
<td>FU, FU/ irinotecan, FU/oxilaplatin</td>
</tr>
<tr>
<td>Safae Ardekani 2012</td>
<td></td>
<td></td>
<td>(FOLFIRI or irinotecan) + cetuximab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS proportions</th>
<th>HR=4.00</th>
<th>HR=2.24</th>
<th>HR=1.82</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
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<td>6 months</td>
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<td>1 year</td>
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<td>2 year</td>
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<td>5 year</td>
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<td>10 year</td>
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**NICE** Used in Company model

**Key:** FU, Fluorouracil

*Source:* ERG critique of company TE response table 1 p5
Encorafenib + cetuximab vs trifluridine-tipiracil:

ERG’s questions validity of naïve comparison

ERG

- RECURSE not restricted to BRAF mutation
- Survival considerably worse than encorafenib + cetuximab
- RECURSE survival curve similar to BEACON trial BRAF V600E mutant control arm
- Raises concerns around naïve comparison and application of BRAF V600E hazard ratio

Source: ERG critique of company technical engagement response p3, figure 1
Encorafenib + cetuximab vs trifluridine-tipiracil: effect of prior treatment regimes on overall survival

*RECOURSE* trial data shows longer OS with increased prior treatments

*ERG* does not use these data

### Company:

- Shows trifluridine-tipiracil more effective with later lines of therapy
- May be explained by presence of good prognostic characteristics

<table>
<thead>
<tr>
<th>Prior regimens</th>
<th>HR for OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1.05 (0.68-1.63)</td>
</tr>
<tr>
<td>3</td>
<td>0.74 (0.51-1.08)</td>
</tr>
<tr>
<td>4+</td>
<td>0.59 (0.47-0.73)</td>
</tr>
</tbody>
</table>

ERG Prefer BEACON control arm as proxy for trifluridine tipiracil: Generalisability of the *RECOURSE* trial to the BEACON population is limited. Substantial differences in treatment history. Confounding variables may differ between prior treatment subgroups

- What is the committee’s view on the *RECOURSE* data as the source for the naïve comparison?
## Encorafenib + cetuximab: summary of clinical effectiveness evidence

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Company</th>
<th>Data used</th>
<th>Rationale</th>
<th>ERG</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI</td>
<td>BEACON control arm with an indirect treatment comparison with assumptions because of no link</td>
<td>BEACON includes cetuximab in comparator arm but not used in practice; ITC adjusts for this</td>
<td>BEACON control arm</td>
<td>Uncertain assumptions needed to form network. Benefit of cetuximab low in BRAF V600E population.</td>
</tr>
<tr>
<td>Trifluridine-tipiracil</td>
<td>Naïve comparison with RECOURSE trial HR applied from Peeters et al for BRAF V600E mutant vs wild type</td>
<td>Best approach with available evidence. RECOURSE trial needs adjusting because population different to BEACON</td>
<td>BEACON control arm</td>
<td>Generalisability of the RECOURSE trial to the BEACON population is limited. Poor outcomes from RESOURCE trial likely biases in favour of encorafenib + cetuximab</td>
</tr>
</tbody>
</table>

Which reflect comparisons that generate valid results?
Cost effectiveness
Overview: how quality-adjusted life years accrue

Improved quality of life

Longer time in progression-free health state

Increased overall survival

Longer length of life

Quality-adjusted life years

Utility values used in company model in response to technical engagement

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Encorafenib + cetuximab</th>
<th>FOLFIRI</th>
<th>Trifluridine- tipiracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>BEACON CRC</td>
<td>BEACON CRC</td>
<td>BEACON CRC average of encorafenib with cetuximab and FOLFIRI with cetuximab</td>
</tr>
<tr>
<td>Progression-free</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
</tr>
<tr>
<td>Post-progression</td>
<td>XXXX</td>
<td>XXXX</td>
<td>XXXX</td>
</tr>
</tbody>
</table>
Company’s model structure

Partitioned survival model, 3 health states

Company’s key assumptions

- Time on treatment = progression free survival
- Post progression survival costs same for all comparators
- Adverse events affect only costs; BEACON EQ-5D measures quality of life
- Vial sharing for intravenous therapy with no wastage.
- Patients do not change treatment in ‘progression free’ health state
- At progression:
  - 1 month of treatment with trifluridine-tipiracil
  - No further treatment after trifluridine-tipiracil

Are these assumptions reasonable?
### Key driver of cost effectiveness: extrapolating overall survival + data source for comparators

<table>
<thead>
<tr>
<th></th>
<th>Base case</th>
<th>ERG sensitivity analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall survival</strong></td>
<td><strong>Data source</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BEACON trial May 2020 data cut, HR from ITC applied for comparator arm</td>
<td></td>
</tr>
<tr>
<td><strong>Extrapolation</strong></td>
<td>Jointly fitted log-logistic to May 2020 data cut</td>
<td>Piecewise exponential to Aug 2019 data cut</td>
</tr>
<tr>
<td><strong>Progression free survival</strong></td>
<td>Jointly fitted log-logistic May 2020</td>
<td>Raw Kaplan-Meier curves using Aug 19</td>
</tr>
<tr>
<td><strong>Time to treatment discontinuation</strong></td>
<td>Assumed equal to progression free survival</td>
<td>None</td>
</tr>
</tbody>
</table>
Overall survival: encorafenib + cetuximab: BEACON CRC

Unplanned data cut from company in response to technical engagement

Data set has been fully validated by the company

BEACON overall survival for encorafenib + cetuximab vs control (August 2019)

BEACON overall survival for encorafenib + cetuximab vs control (May 2020)

Source: company response to technical engagement p13, 15, figure 2 & 3

Does committee consider it appropriate to use the unplanned data cut?
Company’s extrapolation of overall survival: parametric models fitted to encorafenib + cetuximab BEACON data

Selected log-logistic model from goodness of fit, visual comparison and clinical expert input

BEACON May 2020 data cut overall survival

Source: company response to technical engagement p19, figure 6
ERG’s extrapolation of overall survival: parametric models fitted to encorafenib + cetuximab BEACON data

All parametric curves fitted poorly to trial data – piecewise approach preferred
ERG estimates much shorter than company’s

ERG (August 2019 data cut):
- All the curves fitted poorly to trial data
- Cumulative hazard → change of trajectory of hazard rate at 2.8 months
- KM data applied before 2.8 months
- Models after 2.8 months
- Chose exponential model on AIC, BIC, plausibility

Overall survival predictions encorafenib + cetuximab

<table>
<thead>
<tr>
<th>Overall survival predictions encorafenib + cetuximab</th>
<th>% alive at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 yrs</td>
</tr>
<tr>
<td>ERG (Aug 19 data cut) beyond 2.8 months</td>
<td></td>
</tr>
<tr>
<td>Exponential</td>
<td></td>
</tr>
<tr>
<td>Weibull</td>
<td></td>
</tr>
<tr>
<td>Log-normal</td>
<td></td>
</tr>
<tr>
<td>Log-logistic</td>
<td></td>
</tr>
<tr>
<td>Gompertz</td>
<td></td>
</tr>
<tr>
<td>G. gamma</td>
<td></td>
</tr>
<tr>
<td>Company (updated May 2020)</td>
<td></td>
</tr>
<tr>
<td>Log-logistic</td>
<td></td>
</tr>
<tr>
<td>Piecewise log-logistic</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative hazard plot of encorafenib OS data from BEACON CRC trial

Source: ERG report p81, figure 18
Company’s response to technical engagement: extrapolation of overall survival encorafenib + cetuximab

ERG’s piecewise extrapolation appears pessimistic when compared to the observed data

Extrapolation of August 2020 data cut

Company:
BEACON CRC 2020 dataset suggests ERG’s preferred piecewise/exponential curve pessimistic; it estimates 14.7% alive at 2 years and 5.2% alive at 3 years.

ERG – response:
- Little difference between curves by goodness of fit AIC criteria
- Limited information provided for scenarios analyses
- Scenarios using piecewise curves similar to ERG original approach not adequately explored
- Need to explore other suitable curves

Which approach is best to extrapolate overall survival for encorafenib + cetuximab?

Source: company response to technical engagement p16, figure 4

Note: title of graph amended post committee, factual inaccuracy identified by company during meeting. Date in title changed from May 2020 to August 2019
Company’s extrapolation of overall survival & progression free survival: FOLFIRI

Applies hazard ratio from ITC to encorafenib + cetuximab curves to model FOLFIRI

**Company base case:** To model FOLFIRI - Hazard ratio from ITC applied to encorafenib + cetuximab curves – log-logistic

**Company scenario analysis:** clinical experts note limited benefit of cetuximab with FOLFIRI

Scenario provided where OS and PFS of FOLFIRI estimated using BEACON control arm. Company chose log-logistic curve based on AIC/BIC, visual inspection and clinical expert opinion

Source: company submission p109, figures 11 & 12

Note: slide adjusted after committee meeting, factual inaccuracy identified by company. ‘Clinical expert opinion’ added to second box.
ERG’s extrapolation of overall survival: FOLFIRI

Company’s approach varies from considerably from observed BEACON control arm data

ERG: Company’s base case approach (applying HR from ITC) results in estimates that vary considerably from BEACON CRC control arm

Given concerns around ITC, ERG modelled FOLFIRI by fitting curves to control arm of BEACON CRC trial:
- All curves fitted poorly to trial data
- Both arms of the BEACON CRC trial modelled simultaneously using 2.8 months as time 0

Which approach is most appropriate for extrapolating overall survival for FOLFIRI?
- Application of ITC hazard ratio
- Beacon control data – loglogistic extrapolation
- Piecewise approach – exponential curve using 2.8 months as time 0

Company modelling of overall survival and BEACON CRC trial control arm (Aug 2019)

Source ERG report p79, figure 17

<table>
<thead>
<tr>
<th>Overall survival predictions FOLFIRI</th>
<th>% alive at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 yrs</td>
</tr>
<tr>
<td>Company (May 2020)</td>
<td></td>
</tr>
<tr>
<td>Loglogistic</td>
<td>XXX</td>
</tr>
<tr>
<td>HR from ITC</td>
<td></td>
</tr>
<tr>
<td>Loglogistic</td>
<td>XXX</td>
</tr>
<tr>
<td>BEACON data</td>
<td></td>
</tr>
</tbody>
</table>

Source: BEACON data

Exp: Exponential, Weibull, Log-normal, Log-logistic, Gompertz, G. gamma
BEACON results progression free survival 2 data cuts

**Encorafenib + cetuximab vs control**

**August 2019**

Company: Jointly-fitted loglogistic chosen on statistical and visual fit for both August 2019 and May 2020 data cuts

**May 2020**

**Table:**

<table>
<thead>
<tr>
<th>Model</th>
<th>AIC</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exponential</td>
<td>1195.84</td>
<td>1199.23</td>
</tr>
<tr>
<td>Weibull</td>
<td>1193.20</td>
<td>1199.99</td>
</tr>
<tr>
<td>Gompertz</td>
<td>1197.83</td>
<td>1204.62</td>
</tr>
<tr>
<td>Lognormal</td>
<td>1182.59</td>
<td>1189.38</td>
</tr>
<tr>
<td>Generalised gamma</td>
<td>1183.48</td>
<td>1193.67</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>1178.12</td>
<td>1184.91</td>
</tr>
</tbody>
</table>

Source: Company response to technical engagement p15, figure 3

Source: Company submission document B p53, figure 4
ERG extrapolating progression free survival, BEACON control arm

ERG models raw KM data because none of curves offered a good fit to observed data

Parametric survival curves fitted to PFS Aug 19 data for control arm of BEACON

Cumulative hazard of parametric survival curves fitted to PFS data for control arm of BEACON

Source: ERG report p85, figure 20 and 21

Is it appropriate to apply raw KM data to the model or use company extrapolations?
Summary: extrapolating overall survival, progression free survival vs trifluridine-tipiracil

*Key driver of cost effectiveness: extrapolating overall survival + data source for comparators*

<table>
<thead>
<tr>
<th></th>
<th>Base case for trifluridine-tipiracil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Company</strong></td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td>RECOURSE adjusted using HR from Peeters et al 2015</td>
</tr>
<tr>
<td><strong>Extrapolation</strong></td>
<td>Log-logistic</td>
</tr>
<tr>
<td><strong>Progression free survival</strong></td>
<td>Log-logistic extrapolation of RECOURSE data adjusted using HR from Peeters et al 2015</td>
</tr>
</tbody>
</table>
Company’s extrapolating survival: trifluridine-tipiracil
Reconstructs individual patient level data from RECOUSE publication

**Company**: Uses Guyot method then fits parametric models fitted to reconstructed data. Then applies HR applied from Peeters et al. for OS and PFS to adjust for outcomes in BRAF+ population.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BRAF V600E versus BRAF wild-type hazard ratio rounded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>4.0 (2.8, 5.6)</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>3.6 (2.5, 5.0)</td>
</tr>
</tbody>
</table>

OS and PFS curves without BRAF V600E adjustment – total RECOUSE trial population

OS and PFS curves with BRAF V600E adjustment

Source: company submission document B p119, figure 14 and 15
Encorafenib + cetuximab vs trifluridine-tipiracil: ERG’s critique of the naïve comparison (repeated)

Source: ERG critique of company technical engagement response p3, figure 1
Company’s time to treatment discontinuation
encorafenib + cetuximab

*Company assumes equal to progression free survival*

**Company**
- Provides scenario using TTD curve

**ERG**: Company scenario using TTD is counterintuitive, suggests that TTD curve results in lower costs than PFS curve, but KM data shows TTD generally lies above PFS. Possibly because Weibull used for TTD and log-logistic used for PFS.

Progression free survival and time to treatment discontinuation KM curves: encorafenib + cetuximab
August 2019 data cut

Source ERG report p74, figure 15

*What is the best way to model time to treatment discontinuation?*
Drug wastage and relative dose intensities

Company assumes no waste; ERG assume waste

Drug wastage

Company base case assumes vial sharing where possible, based on clinical input. Company provides scenario that assumes vial wastage occurs in 10% patients.

ERG considers company base case wastage assumption inappropriate.

Relative dose intensities (RDI) - ratio of ‘delivered’ to the ‘planned’ dose intensity

Company: base case uses mean RDI and provides scenarios using median RDI. Mean is a better reflection of clinical practice.

ERG: data for RDI from BEACON CRC is skewed, median RDI is higher than the mean, this could be because ‘some patients faring poorly in the early period of the trial’ mean RDI may underestimate cetuximab use.

What is committees view on drug wastage and relative dose intensities?
Technical team opinion:
• Results of BEACON CRC suggest that encorafenib + cetuximab increases survival by at least 3 months compared with comparator arm of the trial.
• Both the company’s and the ERG’s models estimate a survival gain of over 3 months, however the results are uncertain.

What are committee’s views on whether end of life criteria are met?

<table>
<thead>
<tr>
<th>Company</th>
<th>ERG</th>
</tr>
</thead>
</table>
| Does encorafenib + cetuximab extend life by 3 months or more compared with current practice? | • BEACON CRC: median overall survival of 3.4 months for encorafenib + cetuximab vs control chemotherapy  
• Control arm included cetuximab which is expected to have additional benefit vs standard care in UK | • BEACON CRC: risk of bias unclear or high in several domains, magnitude of improvement is uncertain |

Under standard care is the life expectancy of adults with previously treated BRAF-V600E mutation positive metastatic colorectal cancer less than 24 months? | • BEACON CRC: median OS with FOLFIRI or irinotecan + cetuximab = 5.9 months | Literature suggests median survival for previously treated patients with BRAF V600E mutation shorter than 12 months  
ERG agrees patient population meets this criterion |
## Issues resolved after technical engagement

<table>
<thead>
<tr>
<th>Summary</th>
<th>Stakeholder responses</th>
<th>Technical team consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health utilities:</td>
<td>Company amended so utility value for progression free health state</td>
<td>Results more likely to reflect clinical practice</td>
</tr>
<tr>
<td>Costs:</td>
<td>Company amended to cost drugs at start of cycle - as recommended by ERG</td>
<td>Amendments more accurately reflect costs</td>
</tr>
</tbody>
</table>
All ICERs are reported in PART 2 slides because they include confidential PAS discounts for comparators and intervention.
Key issues

1. Treatment pathway:
   – What is the appropriate position in the treatment pathway?
     • 2\textsuperscript{nd} and/or 3\textsuperscript{rd} line?
   – What are the relevant comparators at 2\textsuperscript{nd} line?

2. In absence of a direct comparison, are the results valid from the:
   • indirect treatment comparison?
   • naïve comparison?

3. What are the most appropriate models for extrapolating:
   – Overall survival (OS)
   – Progression-free survival (PFS)

4. How should time to treatment discontinuation (TTD) be modelled?

5. Are the costs included appropriately?

6. Does encorafenib + cetuximab meet NICE’s end of life criteria?
Committee decision making: CDF recommendation criteria

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect data.