Encorafenib (Braftovi®) in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer (mCRC) with a BRAF V600E mutation

**General information**

**Drug description**
Encorafenib is a BRAF inhibitor

**Indication**
Encorafenib is indicated in combination with cetuximab, for the treatment of adult patients with mCRC with a BRAF V600E mutation, who have received prior systemic therapy.

**Current treatment [1]**

- For patients with advanced and mCRC, NICE recommends consideration of one of the following sequences unless contra-indicated:
  - FOLFOX as first-line treatment then single-agent irinotecan as second-line treatment or
  - FOLFOX as first-line treatment then FOLFIRI as second-line treatment or
  - XELOX as first-line treatment then FOLFIRI as second-line treatment.
- Oral therapy with capecitabine is an option for first line treatment of mCRC
- Trifluridine–tipiracil is recommended, within its marketing authorisation and on a patient access scheme, as an option for treating mCRC in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and anti-epidermal growth factor receptor agents, or when these therapies are not suitable.

**Regulatory status**

- **EMA [2]**

  **Approval status for this indication:** On 30 April 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Braftovi®. The CHMP adopted a new indication as follows:
  - Encorafenib is indicated in combination with cetuximab, for the treatment of adult patients with mCRC with a BRAF V600E mutation, who have received prior systemic therapy.
  
  **Other indications:**
  - Encorafenib is indicated in combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

- **FDA [3, 4]**

  **Approval status for this indication:** approved (04/2020); indicated in combination with cetuximab, for the treatment of adult patients with mCRC with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.
  
  **Other indications:**
  - Encorafenib is indicated in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test

**Costs**

42 Braftovi® hard capsules 75 mg = € 1,084.35 [5]

BEACON CRC patients of the **triplet-therapy group** received encorafenib at a dose of 300 mg daily with a median duration of exposure to trial drugs of 21 weeks.

BEACON CRC patients of the **doublet-therapy group** received encorafenib at a dose of 300 mg daily with a median duration of exposure to trial drugs of 19 weeks.

<table>
<thead>
<tr>
<th>Trial name</th>
<th>n</th>
<th>Intervention (Triplet therapy group)</th>
<th>Intervention (Doublet therapy group)</th>
<th>Control group (C)</th>
<th>PE</th>
<th>Characteristic(s)</th>
<th>Biomarker</th>
<th>Funding</th>
<th>Publication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEACON CRC, ARRAY-818-302 NCT02928224 EudraCT number: 2015-005805-35</td>
<td>665</td>
<td><strong>Encorafenib</strong> (300 mg daily), <strong>binimetinib</strong> (45 mg twice daily), and <strong>cetuximab</strong> (400 mg per m² of BSA as an initial dose, then 250 mg per m² weekly)</td>
<td><strong>Encorafenib</strong> and <strong>cetuximab</strong>, administered in the same doses and on the same schedule as the triplet regimen</td>
<td>Patients received the investigators’ choice of either cetuximab (administered in the same doses and on the same schedule as the other regimens) and irinotecan (180 mg per m² on days 1 and 15) or cetuximab and FOLFIRI</td>
<td>The <strong>original sole PE</strong> was OS in the triplet-therapy group as compared with the control group. The protocol was amended to <strong>include an additional PE</strong> of the objective response rate in the triplet-therapy group as compared with the control group.</td>
<td>global, multicenter, randomized, open-label, phase 3 trial</td>
<td>BRFV600E</td>
<td>Link</td>
<td><strong>Array BioPharma and others</strong></td>
</tr>
</tbody>
</table>

**Study characteristics**

**Efficacy** (triplet therapy group vs. doublet therapy group vs. control group)

**Safety** (triplet therapy group vs. doublet therapy group vs. control group)
**Median OS** was 9.0 months (95% CI, 8.0 to 11.4) in the triplet-therapy group and 5.4 months (95% CI, 4.8 to 6.6) in the control group. The risk of death was lower (by 48%) in the triplet-therapy group than in the control group (HR, 0.52; 95% CI, 0.39 to 0.70; p<0.001). Median OS was 8.4 months (95% CI, 7.5 to 11.0) in the doublet-therapy group, and the risk of death was lower than that in the control group (HR, 0.60; 95% CI, 0.45 to 0.79; p<0.001).

**Objective response rate** was higher in the triplet-therapy group than in the control group. The independently reviewed confirmed objective response rate, assessed in the first 331 patients who underwent randomization, was 26% (95% CI, 18 to 35) in the triplet-therapy group and 2% (95% CI, 0 to 7) in the control group (p<0.001). The objective response rate in the doublet-therapy group was 20% (95% CI, 13 to 29), which was also significantly higher than that in the control group (p<0.001).

**Median PFS** was 4.3 months (95% CI, 4.1 to 5.2) in the triplet-therapy group, 4.2 months (95% CI, 3.7 to 5.4) in the doublet-therapy group, and 1.5 months (95% CI, 1.3 to 1.7) in the control group. The HR for disease progression or death was 0.38 (95% CI, 0.29 to 0.49) in the triplet-therapy group as compared with the control group (p<0.001) and 0.40 (95% CI, 0.31 to 0.52) in the doublet-therapy group as compared with the control group (p<0.001).

**Updated analysis, cut-off date 15/08/2020 (doublet vs. triplet therapy group):**

- Median OS: 9.3 months vs. 5.9 months, HR 0.61 (95% CI, 0.48-0.77, p<0.0001)
- Overall response rate (per BIRC): 19.5% vs. 1.8%, p<0.0001
- Median PFS (per BIRC): 4.3 months vs. 1.5 months, HR 0.044 (95% CI 0.35-0.55, p<0.0001)

**Grade ≥3 AEs**:
- In the triplet-therapy group: n=128/222 (58%)
- In the doublet-therapy group: n=108/216 (50%)
- In the control group: n=117/193 (61%)

**Fatal adverse events/Death**: occurred in 4%, 3%, and 4% of the patients, respectively.

**Discontinuation**: 7% of patients in the triplet-therapy group, 8% in the doublet-therapy group, 11% in the control group.

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### ESMO-MCBS version 1.1 (triplet therapy group vs. control group)

<table>
<thead>
<tr>
<th>Scale</th>
<th>Int.</th>
<th>Form</th>
<th>MG ST</th>
<th>MG</th>
<th>HR (95% CI)</th>
<th>Score calculation</th>
<th>PM</th>
<th>Toxicity</th>
<th>QoL</th>
<th>AJ</th>
<th>FM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>NC 2a</td>
<td>s12 m</td>
<td>OS: +3.6 m</td>
<td>OS: 0.52 (0.39-0.70)</td>
<td>HR ≤0.65 AND Gain ≥3 m</td>
<td>4</td>
<td>x</td>
<td>x</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adapated</td>
<td>NC 2a</td>
<td>s12 m</td>
<td>OS: +3.6 m</td>
<td>OS: 0.52 (0.39-0.70)</td>
<td>HR ≤0.65 AND Gain ≥3 m</td>
<td>4</td>
<td>-3% grade 3-4 AEs, -4% DR</td>
<td>x</td>
<td>x</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of bias (study level)

- Adequate generation of randomisation sequence: unclear
- Adequate allocation concealment: unclear
- Blinding: open-label
- Selective outcome reporting unlikely: unclear
- Other aspects which increase the risk of bias: yes
- Risk of bias: high risk

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1. 3 of the deaths were determined by the investigators to be related to treatment: 1 in the triplet-therapy group, 2 in the control group.
2. Discontinuation of therapy primarily because of an AE
3. Trial protocol not available
4. Trial protocol not available
5. BEACON CRC trial is ongoing until 08/2020
6. Industry-funded; interim analysis data; additional primary endpoint amended to the protocol

**Abbreviations**: AE=adverse event, AJ=adjustment, BIRC=blinded independent review committee, BSA=body surface area, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DR=discontinuation rate, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=U.S. Food and Drug Administration, FM=final adjusted magnitude of clinical benefit grade, HR=hazard ratio, Int.=intention, m=months, mCRC=metastatic colorectal cancer, MG=median gain, n=number, SAE=serious adverse event, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary magnitude of clinical benefit grade, QoL=quality of life, ST=standard treatment
References:


