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	Indication
Encorafenib is a BRAF inhibitor	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]	FDA [3, 4]
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. ✓ **Medicine under additional monitoring**	**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.

Study characteristics

Trial name	*n*	Intervention (Triplet therapy group)	Intervention (Doublet therapy group)	Control group (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
BEACON CRC, ARRAY-818-302 NCT02928224 EudraCT number: 2015-005805-35	665	**Encorafenib** (300 mg daily), **binimetinib** (45 mg twice daily), and **cetuximab** (400 mg per m^2 of BSA as an initial dose, then 250 mg per m^2 weekly)	**Encorafenib** and **cetuximab**, administered in the same doses and on the same schedule as the triplet regimen	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 m^2 on days 1 and 15) **or cetuximab and FOLFIRI**	The **original sole PE was OS** in the triplet-therapy group as compared with the control group. The protocol was amended to **include an additional PE** of the objective response rate in the triplet-therapy group as compared with the control group.	global, multicenter, randomized, open-label, phase 3 trial	BRAF V600E	Array BioPharma and others	Link

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, 1.5 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% CIo.35-0.55, p<0.0001)	**Grade ≥3 AEs**: n=128/222 (58%) in the triplet-therapy group, n=108/216 (50%) in the doublet-therapy group, n=117/193 (61%) in the control group. **Fatal adverse events/Death[1]:** occurred in 4%, 3%, and 4% of the patients, respectively. **Discontinuation[2]:** 7% of patients in the triplet-therapy group, 8% in the doublet-therapy group, 11% in the control group

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

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 m	OS: +3.6 m	OS: 0.52 (0.39–0.70)	HR ≤0.65 AND Gain ≥3 m	4	x	x	x	4
Adapted	NC	2a	≤12 m	OS: +3.6 m	OS: 0.52 (0.39–0.70)	HR ≤0.65 AND Gain ≥3 m	4	-3% grade 3-4 AEs, -4% DR	x	x	4

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear[3]	unclear[4]	open-label	unclear[5]	yes[6]	high risk

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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

[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

References:

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2. European Medicines Agency (EMA). Medicines.Braftovi. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/braftovi-0.
3. U.S. Food and Drug Administration (FDA). Drugs@FDA. Braftovi. Label information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210496s006lbl.pdf.
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