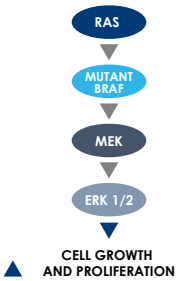
BRAFTOVI® (encorafenib) and cetuximab in *BRAF*^{V600E}-mutant metastatic colorectal cancer (mCRC) May 2020 Fact Sheet

What is BRAFTOVI and how does it work?

BRAFTOVI is an oral small-molecule BRAF kinase inhibitor designed to switch off unwanted signalling in the mitogen-activated protein kinase (MAPK) pathway, which is activated at a constant rate in individuals with *BRAF*-mutant mCRC.[1,2]

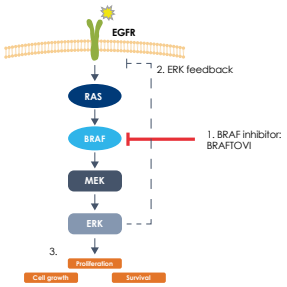
Figure 1: MAPK Signaling Pathway



The MAPK signalling pathway (RAS-RAF-MEK-ERK) is an important pathway that regulates cell growth and survival.[1] Under normal cellular conditions, it is activated in specific cells types (e.g. plasma cells, cells in tear glands) by epidermal growth factor (EGF). The body produces EGF continuously, because it is needed for many cellular processes.[3,4]

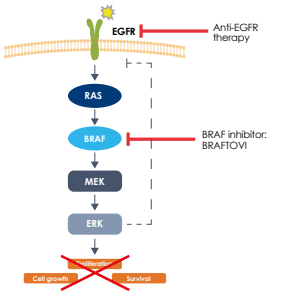
BRAF is a key gene in the MAPK pathway, producing proteins that carry the instructions along the pathway from the EGF receptor (EGFR) on the cell surface to the cell nucleus (or 'control centre').[1,3] EGF signals to the control centre of the cell by activating EGFRs on the cell surface. When EGFRs are not blocked adequately, the control centre still receives messages from 'the outside' telling it to trigger the pathway.[5,6] Faulty mutations in the *BRAF* gene have big implications for CRC, because they can lead to activating the MAPK pathway signalling at a constant rate, and cause unwanted cell division (Figure 1).[1]

Figure 2: MAPK Signaling Pathway and EGFR feedback activation



BRAFTOVI is an inhibitor that blocks BRAF kinase signalling within the MAPK pathway in mCRC cells.[1] Because mCRC tumours have more EGFR on their cell surface than other cancer cell types,[5] some tumours may adapt and overcome the inhibitor and create a 'feedback loop' that reactivates the signalling within the MAPK pathway (Figure 2).[5,6,7]

Figure 3: MAPK Signaling Pathway and EGFR feedback activation



By combining a BRAF kinase inhibitor with an EGFR inhibitor would overcome the feedback activation of EGFR observed in *BRAF*-mutant mCRC, by interrupting the signal and preventing cell division (Figure 3).[5,7-11] Clinical investigators have observed that for mCRC treatment, BRAFTOVI in combination with an anti-EGFR therapy (cetuximab) markedly improved efficacy in preclinical studies.[2,12]

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How does BRAFTOVI in combination with an anti-EGFR therapy (cetuximab) work in advanced *BRAF*^{V600E}-mutant mCRC?

	BRAFTOVI + cetuximab[2]
Investigation	The European Commission granted marketing authorisation for the use of BRAFTOVI in combination with anti-EGFR therapy cetuximab, for the treatment of adult patients with *BRAF*^{V600E}-mutant mCRC, who received prior systemic therapy.
Prognostic and Predictive Marker Testing	Before taking BRAFTOVI, patients must have mCRC with *BRAF*^{V600E} mutation confirmed by a validated test. The efficacy and safety of BRAFTOVI have been established only in patients with CRC tumours expressing *BRAF*^{V600E} mutation. BRAFTOVI should not be used in patients with wild-type *BRAF* CRC.
Administration	The recommended dose of BRAFTOVI is 300 mg (four 75 mg capsules) once daily, when used in combination with cetuximab.
Duration of Treatment	Treatment with BRAFTOVI should be continued until the patient no longer derives benefit or develops unacceptable toxicity.
Efficacy	The BEACON trial demonstrated BRAFTOVI in combination with cetuximab significantly improved overall survival (OS) and objective response rates (ORR), compared with the cetuximab plus irinotecan-containing regimens (Control). • The trial showed a median OS of 9.3 months for patients treated with the doublet combination, compared with 5.9 months for the Control arm (HR 0.61, 95% CI, 0.48–0.77; p<0.0001). • Furthermore, the combination reported an improved ORR (20% vs 2%, p<0.0001), compared with the Control arm.
Safety and Tolerability	The most common adverse drug reactions (>25%) occurring in patients with *BRAF*^{V600E}-mutant mCRC treated with BRAFTOVI in combination with cetuximab were fatigue, nausea, diarrhoea, dermatitis acneiform, abdominal pain, arthralgia/musculoskeletal pain, decreased appetite, rash and vomiting.

Full prescribing information can be found here for BRAFTOVI and here for cetuximab.

BRAFTOVI has been approved in combination with MEKTOVI® (binimetinib) for use in advanced BRAF^{V600}-mutant melanoma.

References

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