THERAPY MANAGEMENT GUIDE

BRAFTOVI in combination with cetuximab

A resource to help support your patients with *BRAF*^{V600E}-mutant mCRC through their treatment

START **MONITOR** **MANAGE**

BRAFTOVI® (encorafenib)

BRAFTOVI is indicated in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.

mCRC, metastatic colorectal cancer.

Recommended starting dose for BRAFTOVI + cetuximab

Instruct your patients about BRAFTOVI administration[1,2]

Once-daily oral therapy	Weekly infusion therapy
BRAFTOVI 300 mg  4 BRAFTOVI capsules (75 mg each)	Cetuximab  **Initial dose: 400 mg/m²** **Subsequent doses: 250 mg/m²** For dosing information for cetuximab, refer to the cetuximab Summary of Product Characteristics.

Continue treatment with BRAFTOVI + cetuximab until disease progression or unacceptable toxicity[1]

May be taken with or without food. Grapefruit juice should be avoided.

Swallow the capsules whole with water.

BRAFTOVI capsules may be opened and the content dispersed in a small quantity of apple sauce (~20 ml) and taken immediately.

Patients should not take a missed dose of BRAFTOVI within **12 hours** of the next dose.

In case of vomiting after administration of BRAFTOVI, the patient should not take an additional dose and should take the next scheduled dose.[1]

Women of childbearing potential must use effective contraception during treatment with BRAFTOVI and for at least 1 month following the last dose. BRAFTOVI may decrease the efficacy of hormonal contraceptives. Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (eg, condom) during treatment with BRAFTOVI and for at least 1 month following the last dose. BRAFTOVI is not recommended during pregnancy and in women of childbearing potential not using contraception. If the patient becomes pregnant while using BRAFTOVI or is already pregnant, the patient should be informed of the potential hazard to the foetus.[1]

It is unknown whether BRAFTOVI or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue BRAFTOVI therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.[1]

There are no data on the effects of BRAFTOVI on fertility in humans. Male patients should be informed of the potential risk for impaired spermatogenesis.[1]

BRAFTOVI is available as 75-mg capsules[1]

BRAFTOVI 75 mg is available in packs of 42 hard capsules, equivalent to 10 days of treatment at full dose.

Not actual size.

Storage for BRAFTOVI[1]

No refrigeration requirement; instruct your patients to store BRAFTOVI below 30°C.

Store in the original package in order to protect from moisture.

Please see accompanying Summary of Product Characteristics.

Dosing in specific populations

Elderly patients[1]

No dose adjustment is required for patients aged 65 years and older (based on age alone).

Hepatic impairment[1]

Degree of hepatic impairment	Child-Pugh score	BRAFTOVI dosing
Mild	A	Use with caution at 300 mg once daily
Moderate	B	Not recommended
Severe	C	

To assess the degree of hepatic impairment, calculate the Child-Pugh score and class.

Child-Pugh score[3]

Variable	Points		
	1	2	3
Hepatic encephalopathy	None	Stage I-II[a]	Stage III-IV[a]
Ascites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/L)	>35	28-35	<28
Prothrombin time (seconds)	<4	4-6	>6

Child-Pugh class[3]

Sum of points	5-6	7-9	10-15
Class	A (mild)	B (moderate)	C (severe)

Renal impairment[1,4]

Degree of renal impairment	BRAFTOVI dosing
Mild (eGFR 60-90 mL/min/1.73 m²)	No dose adjustment required
Moderate (eGFR 30-59 mL/min/1.73 m²)	
Severe (eGFR <30 mL/min/1.73 m²)	No clinical data Use with caution

[a]Stage I may involve a trivial lack of awareness, euphoria or anxiety, a shortened attention span, impairment of the ability to perform addition or subtraction, or an altered sleep rhythm. Stage II may involve lethargy or apathy, time disorientation, obvious personality change, inappropriate behaviour, dyspraxia, or asterixis. Stage III may involve a range of somnolence to a semi-stupor, responsiveness to stimuli, confusion, gross disorientation, or bizarre behaviour. Stage IV entails a coma.[5]

For dosing information for cetuximab, refer to the cetuximab Summary of Product Characteristics.

eGFR, estimated glomerular filtration rate.

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Drug interactions

Effects of other medicinal products on BRAFTOVI[1]

	Effects	Examples
Strong CYP3A4 inhibitors	• Increases BRAFTOVI exposure and potentially increases toxicity • Concomitant administration should be avoided • If unavoidable, carefully monitor safety	ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole, grapefruit juice
Moderate CYP3A4 inhibitors	• Co-administer with caution and carefully monitor safety	amiodarone, erythromycin, fluconazole, diltiazem, amprenavir, imatinib
CYP3A4 inducers	• May result in compromised efficacy • Alternative agents with no or minimal CYP3A induction potential should be considered	carbamazepine, rifampicin, phenytoin, St John's wort

Effects of BRAFTOVI on other medicinal products[1]

	Effects	Examples
CYP3A4 substrates	• May result in increased toxicity or loss of efficacy of CYP3A4 substrates • Co-administer with caution	hormonal contraceptives
UGT1A1 substrates	• May have increased exposure of UGT1A1 substrates • Co-administer with caution	raltegravir, atorvastatin, dolutegravir
Transporter substrates (renal transporters: OAT1, OAT3, OCT2; hepatic transporters: OATP1B1, OATP1B3, OCT1; BCRP) or substrates of P-gp	• May have increased exposure of transporter protein substrates • Co-administer with caution	furosemide, penicillin, atorvastatin, bosentan, methotrexate, rosuvastatin, posaconazole

For drug interaction information for cetuximab, refer to the cetuximab Summary of Product Characteristics.

BCRP, breast cancer resistance protein; CYP3A4, cytochrome P450 3A4; OAT1, organic anion transporter 1; OAT3, organic anion transporter 3; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3; OCT1, organic cation transporter 1; OCT2, organic cation transporter 2; P-gp, permeability glycoprotein; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

Recommendations for monitoring patients before and during treatment with BRAFTOVI + cetuximab

Monitoring at initiation, during, and after treatment helps ensure optimal adverse event management.[1]

Before treatment	During treatment	After treatment
Non-cutaneous malignancy assessments **Head and neck evaluation** **Chest/abdomen CT scan** **Anal and pelvic examinations (for women)** **Complete blood cell counts**	**Non-cutaneous malignancy assessments (as clinically appropriate)** **Head and neck evaluation** **Chest/abdomen CT scan** **Anal and pelvic examinations (for women)** **Complete blood cell counts**	**Non-cutaneous malignancy assessments (as clinically appropriate)** **Head and neck evaluation** **Chest/abdomen CT scan** **Anal and pelvic examinations (for women)** **Complete blood cell counts**
Dermatologic evaluation	**Dermatologic evaluation:** Every 2 months	**Dermatologic evaluation:** For up to 6 months after treatment discontinuation
Blood tests **Liver laboratory values (AST, ALT)**	**Blood tests** **Liver laboratory values:** At least monthly during the first 6 months of treatment, then as clinically indicated **Creatinine values:** As clinically indicated	**Blood tests** **Liver laboratory values:** As clinically indicated **Creatinine values:** As clinically indicated
Cardiac monitoring **ECG** **Electrolyte correction** **QT prolongation risk-factor control**	**Cardiac monitoring** **ECG:** 1 month after initiation and approximately every 3 months thereafter or more frequently as clinically indicated **Electrolyte correction** **QT prolongation risk-factor control**	
	Ophthalmologic evaluation: At each visit for new or worsening visual disturbance and refer for ophthalmologic exam if new or worsening symptoms are found	

For information about monitoring at initiation, during, and after treatment for cetuximab, refer to the cetuximab Summary of Product Characteristics.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computerised tomography; ECG, electrocardiogram.

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Adverse reaction profile of BRAFTOVI + cetuximab

ARs occurring in patients receiving BRAFTOVI + cetuximab (n=216)[1,a]

System organ class	Adverse reaction	Frequency (all grades)
Neoplasms benign, malignant and unspecified	Melanocytic naevus	Very common
	cuSCC[b]	Common
	Skin papilloma[c]	Common
	New primary melanoma[c]	Common
	Basal cell carcinoma	Uncommon
Immune system disorders	Hypersensitivity[d]	Common
Metabolism and nutrition disorders	Decreased appetite	Very common
Psychiatric disorders	Insomnia	Very common
Nervous system disorders	Neuropathy peripheral[c]	Very common
	Headache[c]	Very common
	Dizziness[c]	Common
	Dysgeusia	Common
Cardiac disorders	Supraventricular tachycardia[e]	Common
Vascular disorders	Haemorrhage[f]	Very common
Gastrointestinal disorders	Nausea	Very common
	Vomiting	Very common
	Constipation	Very common
	Abdominal pain[c]	Very common
	Diarrhoea[c]	Very common
	Pancreatitis[c]	Uncommon

Discontinuation rate of all study drugs due to any AR was 1.9% with BRAFTOVI + cetuximab[1]

AR, adverse reaction; cuSCC, cutaneous squamous cell carcinoma.

ARs occurring in patients receiving BRAFTOVI + cetuximab (n=216)[1,a]

System organ class	Adverse reaction	Frequency (all grades)
Skin and subcutaneous disorders	Dermatitis acneiform[c]	Very common
	Rash[c]	Very common
	Dry skin[c]	Very common
	Pruritus[c]	Very common
	Skin hyperpigmentation	Common
	PPES	Common
	Hyperkeratosis[c]	Common
	Alopecia	Common
	Erythema[g]	Common
	Skin exfoliation[h]	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia/musculoskeletal pain[c]	Very common
	Myopathy/muscular disorder[c]	Very common
	Pain in extremity	Very common
	Back pain	Very common
Renal and urinary disorders	Renal failure[c]	Common
General disorders and administration site conditions	Fatigue[c]	Very common
	Pyrexia[c]	Very common
Investigations	Blood creatinine increased[c]	Common
	Transaminase increased[c]	Common
	Amylase increased	Uncommon
	Lipase increased	Uncommon

ARs are listed by MedDRA body system organ class and the following frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

[a]The safety of BRAFTOVI (300 mg orally once daily) in combination with cetuximab (dosed as per its SmPC) was evaluated in 216 patients with *BRAF*^{V600E}-mutant metastatic colorectal cancer. The most common adverse drug reactions (>25%) reported were fatigue, nausea, diarrhoea, dermatitis acneiform, abdominal pain, arthralgia/musculoskeletal pain, decreased appetite, rash, and vomiting.
[b]Includes, but not limited to, keratoacanthoma and squamous cell carcinoma.
[c]Composite terms which included more than one preferred term.
[d]Includes, but not limited to, angioedema, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis, urticaria, and anaphylactic reaction.
[e]Includes but not limited to extrasystoles and sinus tachycardia.
[f]Includes haemorrhage at various sites, including cerebral haemorrhage.
[g]Includes erythema, generalised erythema, plantar erythema.
[h]Includes dermatitis exfoliative, skin exfoliation, exfoliative rash.

PPES, palmar-plantar erythrodysaesthesia syndrome.

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Recommended dose modifications and discontinuations to manage adverse reactions

Dose modifications for BRAFTOVI[1,a]	
Starting dose **300 mg** (four 75-mg capsules)	
▼	
First reduction **225 mg** (three 75-mg capsules)	
▼	
Second reduction **150 mg** (two 75-mg capsules)	
▼	
Permanent discontinuation	

[a]For patients with mild hepatic impairment, administration of BRAFTOVI should be undertaken with caution at the 300-mg dose. In the absence of clinical data, BRAFTOVI is not recommended in patients with moderate to severe hepatic impairment. For patients with severe renal impairment, BRAFTOVI should be taken with caution.

Dose modifications are recommended to manage adverse reactions. Please see Section 4.2 of the full Summary of Product Characteristics for BRAFTOVI for additional information.

For dose modification information for cetuximab, refer to the cetuximab Summary of Product Characteristics.

Dose interruption and discontinuation

Dose interruption[1]

BRAFTOVI	Cetuximab
Interruption	For information on the recommended dose modifications of cetuximab, see section 4.4 of the cetuximab Summary of Product Characteristics

Permanent discontinuation[1]

BRAFTOVI		Cetuximab
Permanent discontinuation	▶	Discontinuation
Discontinuation	◀	Permanent discontinuation

If BRAFTOVI is permanently discontinued, cetuximab should be discontinued.[1]
If cetuximab is permanently discontinued, BRAFTOVI should be discontinued.[1]

For dose modifications information for cetuximab, refer to the cetuximab Summary of Product Characteristics.

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Managing adverse reactions during treatment with BRAFTOVI + cetuximab

Adverse reaction[1]	Severity of adverse reaction[1,a]	Dose modifications for BRAFTOVI[1]
Skin and subcutaneous		
Cutaneous reactions	Grade 2	**Maintain dose** · If rash worsens or does not improve within 2 weeks with treatment, withhold until Grade 0 or 1 and then resume at same dose
	Grade 3	**Withhold until improved to Grade 0 or 1** · If first occurrence, resume at same dose · If recurrent Grade 3, resume at a reduced dose
	Grade 4	**Permanently discontinue.**
PPES	Grade 2	**Maintain dose and institute supportive measures such as topical therapy** · If not improved within 2 weeks, withhold until improved to Grade 0 or 1 and then resume at same dose level or a reduced dose
	Grade 3	**Withhold, institute supportive measures such as topical therapy, and reassess weekly** · When improved to Grade 0 or 1, resume at same dose level or a reduced dose

Maintain or withhold **Reduce or withhold** **Permanently discontinue**

If BRAFTOVI is permanently discontinued, cetuximab should be discontinued.[1]
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PPES, palmar-plantar erythrodysaesthesia syndrome.

Adverse reaction[1]	Severity of adverse reaction[1,a]	Dose modifications for BRAFTOVI[1]
Ocular		
Uveitis including iritis and iridocyclitis	Grades 1-3	**Withhold and conduct ophthalmic monitoring within 2 weeks for Grade 1 or 2 uveitis that doesn't respond to ocular therapy or for Grade 3 uveitis** · If Grade 1 uveitis improves to Grade 0, then resume at the same dose · If Grade 2 or 3 uveitis improves to Grade 0 or 1, then treatment should be resumed at a reduced dose
		If not improved within 6 weeks, repeat ophthalmic monitoring and permanently discontinue.
	Grade 4	**Permanently discontinue and follow up with ophthalmologic monitoring.**
Cardiac		
QTc prolongation	QTcF >500 ms and change ≤60 ms from pre-treatment value	**Withhold** · When QTcF returns to ≤500 ms, resume at a reduced dose · If more than 1 recurrence, discontinue
		· If more than 1 recurrence, discontinue
	QTcF >500 ms and increased by >60 ms from pre-treatment value	**Permanently discontinue.**

Maintain or withhold **Reduce or withhold** **Permanently discontinue**

[a]Grades per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

QTc, QT interval corrected; QTcF, QT interval corrected by Fridericia's formula.

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Managing adverse reactions during treatment with BRAFTOVI + cetuximab (cont)

Adverse reaction[1]	Severity of adverse reaction[1,a]	Dose modifications for BRAFTOVI[1]
Liver laboratory abnormalities		
AST or ALT	**Grade 2** (AST or ALT >3x - ≤5x ULN)	**Maintain dose** • If no improvement within 4 weeks, withhold until improved to Grade 0 or 1 or to pre-treatment/baseline levels and then resume at same dose
	First occurrence of Grade 3 (AST or ALT >5x ULN and blood bilirubin >2x ULN)	**Withhold for up to 4 weeks** • If improved to Grade 0 or 1 or baseline levels, resume at a reduced dose
		If not improved, permanently discontinue.
	First occurrence of Grade 4 (AST or ALT >20 ULN)	**Withhold for up to 4 weeks** • If improved to Grade 0 or 1 or baseline levels, resume at a reduced dose
		If not improved, permanently discontinue. **OR** **Permanently discontinue.**
	Recurrent Grade 3 (AST or ALT >5x ULN and blood bilirubin >2x ULN)	**Consider permanently discontinuing.**
	Recurrent Grade 4 (AST or ALT >20 ULN)	**Permanently discontinue.**

Adverse reaction[1]	Severity of adverse reaction[1,a]	Dose modifications for BRAFTOVI[1]
Other		
	Recurrent or intolerable Grade 2 adverse reactions **OR** **First occurrence of Grade 3 adverse reactions**	**Withhold for up to 4 weeks** • If not improved to Grade 0 or 1 or to baseline levels, resume at a reduced dose
		If not improved, permanently discontinue.
	First occurrence of any Grade 4 adverse reactions	**Withhold for up to 4 weeks** • If improved to Grade 0 or 1 or baseline levels, resume at a reduced dose
		If not improved, permanently discontinue. **OR** **Permanently discontinue.**
	Recurrent Grade 3 adverse reactions	**Consider permanently discontinuing.**
	Recurrent Grade 4 adverse reactions	**Permanently discontinue.**
Non-cutaneous malignancy: Non-cutaneous *RAS* mutation–positive malignancies	**Consider permanently discontinuing.**	

Maintain or withhold **Reduce or withhold** **Permanently discontinue**

[a]Grades per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

If BRAFTOVI is permanently discontinued, cetuximab should be discontinued.[1]
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THERAPY MANAGEMENT GUIDE

For BRAFTOVI in combination with cetuximab

START

Recommended starting dose and administration of BRAFTOVI: 300 mg orally once daily and may be taken with or without food.[a] Grapefruit juice should be avoided[1]

No dose adjustment is required for patients aged 65 years and older (based on age alone)[1]

No refrigeration requirement; instruct your patients to store BRAFTOVI below 30˚C[1]

[a]Starting dose depending on dose adjustments in certain populations.

MONITOR

Monitoring patients through certain tests and clinical evaluations is recommended prior to, during, and after treatment with BRAFTOVI + cetuximab[1]

MANAGE

Dose modifications are recommended to manage adverse reactions[1]

Please refer your patients to the BRAFTOVI Patient Brochure and the complete patient information leaflet in their medication packaging for further information and guidance.

For information about dosing and adverse events for cetuximab, refer to the cetuximab Summary of Product Characteristics.

References: 1. Braftovi Summary of Product Characteristics. Pierre Fabre Médicament, 2020. **2.** Erbitux Summary of Product Characteristics. Merck Europe B.V., 2020. **3.** Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open*. 2016:1(2)e000042. doi:10.1136/esmoopen-2016-000042. **4.** European Medicines Agency. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-decreased-renal-function_en.pdf. Published 17 December 2015. Accessed 9 March 2020. **5.** Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60(2):715-735.

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