PHYSICIAN PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT

Braftovi 75 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 75 mg of encorafenib

For the full list of excipients, *see Description (10)*.

PHARMACEUTICAL FORM

Hard capsule

1 THERAPEUTIC INDICATIONS

1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

BRAFTOVI® - encorafenib is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation *[see Dosage and Administration (2.1)]*.

1.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

BRAFTOVI is indicated, in combination with cetuximab and mFOLFOX6, for the treatment of patients with metastatic colorectal cancer (mCRC) with a BRAF V600E mutation, as detected by an approved test [see Dosage and Administration (2.1)].

BRAFTOVI® - encorafenib is indicated, in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an approved test, after prior therapy *[see Dosage and Administration (2.1)]*.

1.3 BRAF V600E Mutation-Positive metastatic non-small cell lung cancer (NSCLC)

BRAFTOVI® - encorafenib is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) adenocarcinoma with a BRAF V600E mutation, as detected by an approved test.

1.4 Limitations of Use

BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma, wild-type BRAF CRC, or wild-type BRAF NSCLC *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (13.1)]*.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

Confirm the presence of a BRAF V600E mutation in tumor specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (13.2))]*

BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

Confirm the presence of a BRAF V600E mutation in tumor or plasma specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (13.3)]*. If no mutation is detected in a plasma specimen, test tumor tissue.

2.2 Recommended Dosage for BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma and for BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

The recommended dosage of BRAFTOVI is 450 mg (six 75 mg capsules) orally once daily in combination with binimetinib until disease progression or unacceptable toxicity. Refer to the binimetinib prescribing information for recommended binimetinib dosing information.

2.3 Recommended Dosage for BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

2.4 The recommended dosage of BRAFTOVI is 300 mg (four 75 mg capsules) orally once daily in combination with biweekly cetuximab and mFOLFOX6 (fluorouracil, leucovorin and oxaliplatin) [see Clinical Studies (13.2)] or in combination with weekly cetuximab [see Clinical Studies (13.3)] until disease progression or unacceptable toxicity. Administration

BRAFTOVI may be taken with or without food *[see Clinical Pharmacology (11.3)]*. Do not take a missed dose of BRAFTOVI within 12 hours of the next dose of BRAFTOVI.

Do not take an additional dose if vomiting occurs after BRAFTOVI administration but continue with the next scheduled dose.

2.5 Dosage Modifications for Adverse Reactions or BRAF V600E Mutation-Positive Metastatic NSCLC

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

If binimetinib is withheld, reduce BRAFTOVI to a maximum dose of 300 mg (four 75 mg capsules) once daily until binimetinib is resumed *[see Warnings and Precautions (0)]*.

Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 1.

Table 1: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions – Melanoma or NSCLC

Action	Recommended Dose
First Dose Reduction	300 mg (four 75 mg capsules) orally once daily
Second Dose Reduction	225 mg (three 75 mg capsules) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate BRAFTOVI 225 mg (three 75 mg capsules) once daily

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

If cetuximab is discontinued, discontinue BRAFTOVI.

Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 2.

Table 2: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions – CRC

Action	Recommended Dose
First Dose Reduction	225 mg (three 75 mg capsules) orally once daily
Second Dose Reduction	150 mg (two 75 mg capsules) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate BRAFTOVI 150 mg (two 75 mg capsules) once daily

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma and BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC), or BRAF V600E Mutation-Positive NSCLC

Dosage modifications for adverse reactions associated with BRAFTOVI are presented in Table 3.

Table 3: Recommended Dosage Modifications for BRAFTOVI for Adverse Reactions

Severity of Adverse Reaction[a]	Dose Modification for BRAFTOVI
New Primary Malignancies [see Warnings and Precautions (5.1)]	
Non-Cutaneous RAS Mutation-positive Malignancies	Permanently discontinue BRAFTOVI.
Hepatotoxicity [see Warnings and Precautions (5.4)]	
• Grade 2 AST or ALT increased	Maintain BRAFTOVI dose. • If no improvement within 4 weeks, withhold BRAFTOVI until improves to Grade 0-1 or to pretreatment/baseline levels and then resume at same dose.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions.
Uveitis [see Warnings and Precautions (0)]	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold BRAFTOVI for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue BRAFTOVI.
• Grade 4	Permanently discontinue BRAFTOVI.
QTc Prolongation [see Warnings and Precautions (0)]	
• QTcF greater than 500 ms and less than or equal to 60 ms increase from baseline	Withhold BRAFTOVI until QTcF less than or equal to 500 ms. Resume at reduced dose. • If more than one recurrence, permanently discontinue BRAFTOVI.
• QTcF greater than 500 ms and greater than 60 ms increase from baseline	Permanently discontinue BRAFTOVI.
•	•
•	
Dermatologic [other than Hand-foot Skin Reaction (HFSR)] [see Adverse Reactions (6.1)]	
• Grade 2	If no improvement within 2 weeks, withhold BRAFTOVI until Grade 0-1. Resume at same dose.
• Grade 3	Withhold BRAFTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue BRAFTOVI.
Other Adverse Reactions (including Hemorrhage) [see Warnings and Precautions (0)] and HFSR[see Adverse Reactions (6.1)][b]	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• First occurrence of any Grade 4	Permanently discontinue BRAFTOVI or Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, then resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• Recurrent Grade 3	Consider permanently discontinuing BRAFTOVI.
• Recurrent Grade 4	Permanently discontinue BRAFTOVI.

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

[b] Dose modification of BRAFTOVI when administered with binimetinib or with cetuximab is not recommended for new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; creatine phosphokinase (CPK) elevation; rhabdomyolysis; and venous thromboembolism.

Refer to the binimetinib or cetuximab prescribing information for dose modifications for adverse reactions associated with each product, as appropriate.

2.6 Dose Modifications for Coadministration With Strong or Moderate CYP3A4 Inhibitors

Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors. If coadministration is unavoidable, reduce the BRAFTOVI dose according to the recommendations in Table 4. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the BRAFTOVI dose that was taken prior to initiating the CYP3A4 inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (11.3)]*.

Table 4: Recommended Dose Reductions for BRAFTOVI for Coadministration With Strong or Moderate CYP3A4 Inhibitors

Current Daily Dose[a]	Dose for Coadministration with Moderate CYP3A4 Inhibitor	Dose for Coadministration with Strong CYP3A4 Inhibitor
450 mg	225 mg (three 75 mg capsules)	150 mg (two 75 mg capsules)
300 mg	150 mg (two 75 mg capsules)	75 mg
225 mg	75 mg	75 mg
150 mg	75 mg	75 mg[b]

[a] Current daily dose refers to recommended dose of BRAFTOVI based on indication or reductions for adverse reactions based on dosing recommendations in Table 1 (Melanoma) and Table 2 (CRC).

[b] Encorafenib exposure at the 75 mg QD BRAFTOVI dosage when coadministered with a strong CYP3A4 inhibitor is expected to be higher than at the 150 mg QD dosage in the absence of a CYP3A4 inhibitor and similar to exposure at the 225 mg QD dosage in the absence of a CYP3A4 inhibitor. Monitor patients closely for adverse reactions and use clinical judgement when using BRAFTOVI with strong CYP3A4 inhibitors at the 150 mg dose level.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 75 mg, hard gelatin, stylized "A" on the cap and "LGX 75 mg" on the body.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in *Description (10)*.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur with BRAFTOVI.

Cutaneous Malignancies

In COLUMBUS, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6%, and basal cell carcinoma occurred in 1.6% of patients who received BRAFTOVI in combination with binimetinib. Median time to first occurrence of cuSCC/KA was 5.8 months (range 1 to 9 months) *[see Adverse Reactions (6.1)]*.

For patients who received BRAFTOVI as a single agent, cuSCC/KA was reported in 8%, basal cell carcinoma in 1%, and a new primary melanoma in 5% of patients.

In BEACON CRC, cuSCC/KA occurred in 1.4% of patients with CRC, and a new primary melanoma occurred in 1.4% of patients who received BRAFTOVI in combination with cetuximab.

In PHAROS, cuSCC and skin papilloma, each occurred in 2% of patients who received BRAFTOVI in combination with binimetinib.

In BREAKWATER, skin papilloma was reported in 2.6%, basal cell carcinoma in 1.3%, squamous cell carcinoma of skin in 0.9%, keratoacanthoma in 0.4% and malignant melanoma in situ in 0.4% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6.

Perform dermatologic evaluations prior to initiating treatment, every 2 months during treatment, and for up to 6 months following discontinuation of treatment. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Dose modification is not recommended for new primary cutaneous malignancies.

Non-Cutaneous Malignancies

Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies *[see Dosage and Administration (2.5)]*.

5.2 Tumor Promotion in BRAF Wild-Type Tumors

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells, which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation prior to initiating BRAFTOVI *[see Therapeutic indications (1), Dosage and Administration (2.1)]*.

5.3 Cardiomyopathy

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients treated with BRAFTOVI in combination with binimetinib. In COLUMBUS, evidence of cardiomyopathy (decreased in LVEF below the institutional LLN with an absolute decreased in LVEF ≥10% below baseline as detected by echocardiography or MUGA) occurred in 7% of patients receiving BRAFTOVI plus binimetinib. Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) in patients receiving BRAFTOVI in combination with binimetinib was 3.6 months (range 0 to 21 months). Cardiomyopathy resolved in 87% of patients receiving BRAFTOVI plus binimetinib.

In PHAROS, evidence of cardiomyopathy (decrease in LVEF below the institutional LLN with an absolute decrease in LVEF ≥10% below baseline as detected by echocardiography or MUGA) occurred in 11% of patients receiving BRAFTOVI in combination with binimetinib. Grade 3 left ventricular dysfunction occurred in 1% of patients. Cardiomyopathy resolved in 82% of patients receiving BRAFTOVI plus binimetinib.

Assess ejection fraction by echocardiogram or MUGA scan prior to initiating treatment, one month after initiating treatment, and every 2 to 3 months during treatment. The safety of BRAFTOVI in combination with binimetinib has not been established in patients with baseline ejection fraction that is either below 50% or below the institutional lower limit of normal (LLN). Patients with cardiovascular risk factors should be monitored closely when treated with BRAFTOVI.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.4 Hepatotoxicity

Hepatotoxicity can occur when BRAFTOVI is administered in combination with binimetinib. In COLUMBUS, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving BRAFTOVI in combination with binimetinib was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase.

In PHAROS, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving BRAFTOVI in combination with binimetinib was 10% for AST, 9% for ALT, and 3.2% for alkaline phosphatase.

In BREAKWATER, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6 was 2.2% for alkaline phosphatase, 1.3% for ALT, and 0.9% for AST.

Monitor liver laboratory tests before initiation of BRAFTOVI, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.5 Hemorrhage

In COLUMBUS, hemorrhage occurred in 19% of patients receiving BRAFTOVI in combination with binimetinib; Grade 3 or greater hemorrhage occurred in 3.2% of patients. The most frequent hemorrhagic

events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%). Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients.

In BEACON CRC, hemorrhage occurred in 19% of patients receiving BRAFTOVI in combination with cetuximab; Grade 3 or higher hemorrhage occurred in 1.9% of patients, including fatal gastrointestinal hemorrhage in 0.5% of patients. The most frequent hemorrhagic events were epistaxis (6.9%), hematochezia (2.3%) and rectal hemorrhage (2.3%).

In PHAROS, hemorrhage occurred in 12% of patients receiving BRAFTOVI in combination with binimetinib including fatal hemorrhage intracranial (1%); Grade 3 or 4 hemorrhage occurred in 4.1% of patients. The most frequent hemorrhagic events were anal hemorrhage and hemothorax (2% each).

In BREAKWATER, hemorrhage occurred in 30% of patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6; Grade 3 or 4 hemorrhage occurred in 3% of patients.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5), Adverse Reactions (6.1)]*.

5.6 Uveitis

Uveitis, including iritis and iridocyclitis, has been reported in patients treated with BRAFTOVI in combination with binimetinib. In COLUMBUS, the incidence of uveitis among patients treated with BRAFTOVI in combination with binimetinib was 4%. In PHAROS, the incidence of uveitis among patients treated with BRAFTOVI in combination with binimetinib was 1%.

Assess for visual symptoms at each visit. Perform an ophthalmologic evaluation at regular intervals and for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5), Adverse Reactions (6.1)]*.

5.7 QT Prolongation

BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients *[see Clinical Pharmacology (11.2)]*. In COLUMBUS, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination with binimetinib. In PHAROS, an increase in QTcF to >500 ms was measured in 2.1% (2/95) of patients who received BRAFTOVI in combination with binimetinib.
In BREAKWATER, an increase of QTcF >500 ms was measured in 3.6% (8/222) of patients receiving BRAFTOVI in combination with cetuximab and mFOLFOX6.

Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc > 500 ms *[see Dosage and Administration (2.5), Adverse Reactions (6.1)]*.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman. Encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the recommended dose of 450 mg, with no clear findings at lower doses.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use an effective, non-hormonal method of contraception since BRAFTOVI can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the last dose of BRAFTOVI *[see Use in Specific Populations (8.1, 8.3)]*.

5.9 Risks Associated with BRAFTOVI as a Single Agent

BRAFTOVI when used as a single agent is associated with an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with binimetinib. In COLUMBUS, Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% of patients treated with BRAFTOVI in combination with binimetinib *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

If binimetinib is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended *[see Dosage and Administration (2.5)]*.

5.10 Risks Associated with Combination Treatment

BRAFTOVI is indicated for use as part of a regimen in combination with binimetinib, in combination with cetuximab, or in combination with cetuximab and mFOLFOX6. Refer to the prescribing information for binimetinib, cetuximab and individual product components of mFOLFOX6 for additional risk information.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Tumor Promotion in BRAF Wild-Type Tumors *[see Warnings and Precautions (5.2)]*
- Cardiomyopathy [see Warnings and Precautions *(5.3)*]
- Hepatotoxicity [see Warnings and Precautions *(5.4)*]
- Hemorrhage *[see Warnings and Precautions (0)]*
- Uveitis *[see Warnings and Precautions (0)]*
- QT Prolongation *[see Warnings and Precautions (0)]*
- Embryo-Fetal Toxicity [see Warnings and Precautions (*5.8*)]
- Risks Associated with BRAFTOVI as a Single Agent *[see Warnings and Precautions (5.9)]*
- Risks Associated with Combination Treatment *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

The safety of BRAFTOVI in combination with binimetinib is described in 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAFTOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS).

The COLUMBUS trial *[see Clinical Studies (13.1)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 11.8 months for patients treated with BRAFTOVI in combination with binimetinib and 6.2 months for patients treated with vemurafenib.

The most common (≥ 25%) adverse reactions in patients receiving BRAFTOVI in combination with binimetinib were fatigue, nausea, vomiting, abdominal pain, and arthralgia.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with binimetinib; the most common were nausea (7%), vomiting (7%), and pyrexia (4%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 14% of patients receiving BRAFTOVI in combination with binimetinib; the most common were arthralgia (2%), fatigue (2%), and nausea (2%). Five percent (5%) of patients receiving BRAFTOVI in combination with binimetinib experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI; the most common were hemorrhage in 2% and headache in 1% of patients.

Table 5 and Table 6 present adverse drug reactions and laboratory abnormalities, respectively, identified in COLUMBUS. The COLUMBUS trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for BRAFTOVI in combination with binimetinib, as compared to vemurafenib, for any specific adverse reaction listed in Table 5.

Table 5: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination With Binimetinib in COLUMBUS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	43	3	46	6
Pyrexia[c]	18	4	30	0
Gastrointestinal Disorders				
Nausea	41	2	34	2
Vomiting[c]	30	2	16	1
Abdominal pain[c]	28	4	16	1
Constipation	22	0	6	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[c]	26	1	46	6
Myopathy[c]	23	0	22	1
Pain in extremity	11	1	13	1
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis[c]	23	1	49	1
Rash[c]	22	1	53	13
Dry skin[c]	16	0	26	0
Alopecia[c]	14	0	38	0
Pruritus[c]	13	1	21	1
Nervous System Disorders				
Headache[c]	22	2	20	1
Dizziness[c]	15	3	4	0
Peripheral neuropathy[c]	12	1	13	2
Vascular Disorders				
Hemorrhage[c]	19	3	9	2

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Grade 4 adverse reactions limited to fatigue (n=1), pruritus (n=1) and rash (n=1) in the BRAFTOVI with binimetinib arm.
[c] Represents a composite of multiple, related preferred terms.

BRAFTOVI when used as a single agent increases the risk of certain adverse reactions compared to BRAFTOVI in combination with binimetinib. In patients receiving BRAFTOVI 300 mg orally once daily as a single agent, the following adverse reactions were observed at a higher rate (≥ 5%) compared to patients receiving BRAFTOVI in combination with binimetinib: palmar-plantar erythrodysesthesia syndrome (51% vs. 7%), hyperkeratosis (57% vs. 23%), dry skin (38% vs. 16%), erythema (16% vs. 7%), rash (41%

vs. 22%), alopecia (56% vs. 14%), pruritus (31% vs. 13%), arthralgia (44% vs. 26%), myopathy (33% vs. 23%), back pain (15% vs. 9%), dysgeusia (13% vs. 6%), and acneiform dermatitis (8% vs. 3%).

Other clinically important adverse reactions occurring in <10% of patients who received BRAFTOVI in combination with binimetinib were:

Nervous system disorders: *Facial paresis*

Gastrointestinal disorders: *Pancreatitis*

Skin and subcutaneous tissue disorders: *Panniculitis, Photosensitivity*

Immune system disorders: *Drug hypersensitivity*

Table 6: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Receiving BRAFTOVI in Combination With Binimetinib in COLUMBUS[a]

Laboratory Abnormality	BRAFTOVI with binimetinib[a] N=192		Vemurafenib[a] N=186	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	36	3.6	34	2.2
Leukopenia	13	0	10	0.5
Lymphopenia	13	2.1	30	7
Neutropenia	13	3.1	4.8	0.5
Chemistry				
Increased Creatinine	93	3.6	92	1.1
Increased Gamma Glutamyl Transferase	45	11	34	4.8
Increased ALT	29	6	27	2.2
Increased AST	27	2.6	24	1.6
Hyperglycemia	28	5	20	2.7
Increased Alkaline Phosphatase	21	0.5	35	2.2
Hyponatremia	18	3.6	15	0.5
Hypermagnesemia	10	1.0	26	0.5

[a] Grades per National Cancer Institute CTCAE v4.03.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (mCRC) in combination with Cetuximab and mFOLFOX6

The safety of BRAFTOVI 300 mg once daily in combination with cetuximab (500 mg/m2 every 2 weeks) and mFOLFOX6 was evaluated in 231 patients with BRAF V600E mutation-positive metastatic CRC in a randomized, open-label, active-controlled trial (BREAKWATER) [see Clinical Studies (13.2)]. BREAKWATER excluded patients with pancreatitis, leptomeningeal disease, chronic inflammatory bowel disease requiring medical intervention, as well as clinically significant cardiovascular diseases [e.g., myocardial infarction, acute coronary syndromes, NYHA Class ≥II congestive heart failure, prolonged QTcF interval (≥480 ms), history of prolonged QT syndrome] and active infectious conditions. Among patients who received BRAFTOVI, 54% were exposed for 6 months or longer and 18% were exposed for one year or longer. Serious adverse reactions occurred in 38% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6. Serious adverse reactions in >3% of patients included intestinal obstruction and pyrexia (3.5% each). Fatal gastrointestinal perforation occurred in 0.9% of patients who received BRAFTOVI in combination with cetuximab and mFOLFOX6. Permanent

discontinuation of BRAFTOVI due to an adverse reaction occurred in 12% of patients. Adverse reactions which resulted in permanent discontinuation of BRAFTOVI in ≥1% of patients included increased lipase. Dosage interruptions of BRAFTOVI due to an adverse reaction occurred in 57% of patients. Adverse reactions which required dosage interruption in ≥5% included decreased neutrophil count, pyrexia, and anemia. Dose reductions of BRAFTOVI due to an adverse reaction occurred in 22% of patients. Adverse reactions leading to dose reductions of BRAFTOVI in ≥2% of patients included increased lipase, nausea, and vomiting. Reference ID: 554802313 The most common (≥25%) adverse reactions of BRAFTOVI when used in combination with cetuximab and mFOLFOX6 were peripheral neuropathy, nausea, fatigue, rash, diarrhea, decreased appetite, vomiting, hemorrhage, abdominal pain, and pyrexia. The most common Grade 3 or 4 laboratory abnormalities (≥10%) of BRAFTOVI when used in combination with cetuximab and mFOLFOX6 were increased lipase, decreased neutrophil count, decreased hemoglobin, decreased white blood cell count, and increased glucose. Table 7 and Table 8 present adverse drug reactions and laboratory abnormalities, respectively, identified in BREAKWATER.

Table 7: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Cetuximab and mFOLFOX6 in BREAKWATER

Adverse Reaction	BRAFTOVI with cetuximab and mFOLFOX6 N=231		mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab N=228	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Nervous System Disorders				
Peripheral neuropathy[b]	62	15	53	6
Headache	13	<1	7	0
Dysgeusia	12	0	14	0
Neurotoxicity	11	5	8	0
Gastrointestinal Disorders				
Nausea	51	3	48	3
Diarrhea	34	1	47	4
Vomiting	33	4	21	2
Abdominal pain[b]	26	4	27	1
Constipation	20	<1	19	<1
General Disorders and Administration Site Conditions				
Fatigue[b]	49	7	38	4
Pyrexia[b]	26	2	14	<1
Metabolism and Nutrition Disorders				
Decreased appetite	33	2	25	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[b]	23	1	4	0
Myopathy[b]	14	0	7	<1
Skin and Subcutaneous Tissue Disorders				
Rash[b]	31	1	4	0
Alopecia	21	0	10	0
Dry skin[b]	17	0	4	0
Dermatitis acneiform[b]	17	1	1	0
Skin hyperpigmentation	17	0	2	0
Pruritus	11	0	3	<1

Table 7: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Cetuximab and mFOLFOX6 in BREAKWATER[a]

Adverse Reaction	BRAFTOVI with cetuximab and mFOLFOX6 N=231		mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab N=228	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Vascular Disorders				
Hemorrhage[b]	30	3	18	1
Psychiatric Disorder				
Insomnia[b]	11	0	7	0

a. Grades per National Cancer Institute CTCAE v4.03.
b. Represents multiple related terms.

Table 8: Laboratory Abnormalities Occurring in ≥20% (All Grades) of Patients Receiving BRAFTOVI in Combination with Cetuximab and mFOLFOX6 in BREAKWATER[a]

Laboratory Abnormality[b]	BRAFTOVI with cetuximab and mFOLFOX6		mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophil count decreased	63	36	60	34
White blood cell decreased	62	12	54	7
Hemoglobin decreased	60	13	47	5
Platelet count decreased	60	1	50	2
Activated partial thromboplastin time prolonged	57	3	38	1
INR increased	39	1	20	1
Chemistry				
Lipase increased	82	51	54	25
Creatinine increased	64	1	67	1
Glucose increased	49	11	35	2
Alanine aminotransferase increased	38	1	40	2
Albumin decreased	36	0	24	1
Aspartate aminotransferase increased	36	1	35	2
Potassium decreased	33	4	19	4
Alkaline phosphatase increased	31	2	31	1
Calcium decreased	24	4	16	2
Magnesium decreased	23	1	11	1

a. Grades per National Cancer Institute CTCAE v4.03.
b. The denominator used to calculate the rate varied from 220 to 227 based on the number of patients with a baseline and at least one post-treatment value.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

The safety of BRAFTOVI 300 mg once daily in combination with cetuximab (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly) was evaluated in 216 patients with BRAF V600E mutation-positive metastatic CRC in a randomized, open-label, active-controlled trial (BEACON CRC). The BEACON CRC trial *[see Clinical Studies (13.2)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (> 480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 4.4 months for patients treated with BRAFTOVI in combination with cetuximab and 1.6 months for patients treated with either irinotecan or infusional 5-fluorouracil (5-FU)/folinic acid (FA)/irinotecan (FOLFIRI) in combination with cetuximab.

The most common (≥ 25%) adverse reactions in patients receiving BRAFTOVI in combination with cetuximab were fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia, and rash.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 33% of patients receiving BRAFTOVI in combination with cetuximab; the most common were vomiting (4%), fatigue (4%), nausea (4%), pyrexia (3%), and diarrhea (3%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 9% of patients receiving BRAFTOVI in combination with cetuximab; the most common were fatigue (2%), arthralgia (2%), and peripheral neuropathy (2%). Ten percent (10%) of patients receiving BRAFTOVI in combination with cetuximab experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI. None of the adverse reactions leading to permanent discontinuation of BRAFTOVI occurred in more than one patient (>0.5%).

Table and Table present adverse drug reactions and laboratory abnormalities, respectively, identified in BEACON CRC.

Table 9: Adverse Reactions Occurring in ≥ 10% of Patients Receiving BRAFTOVI in Combination With Cetuximab in BEACON CRC[a]

Adverse Reaction	BRAFTOVI with cetuximab N=216		Irinotecan with cetuximab or FOLFIRI with cetuximab N=193	
	All Grades (%)	≥ Grade 3[b] (%)	All Grades (%)	≥ Grade 3 (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	51	7	50	8
Pyrexia[c]	17	1	15	1
Gastrointestinal Disorders				
Nausea	34	1	41	1
Diarrhea[c]	33	2	48	10
Abdominal pain[c]	30	4	32	5
Vomiting	21	1	29	3
Constipation	15	0	18	1
Metabolism and Nutrition Disorders				
Decreased appetite	27	1	27	3
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[c]	27	1	3	0
Myopathy[c]	15	1	4	0
Pain in extremity	10	0	1	0
Skin and Subcutaneous Tissue Disorders				

Table 9: Adverse Reactions Occurring in ≥ 10% of Patients Receiving BRAFTOVI in Combination With Cetuximab in BEACON CRC[a]

Adverse Reaction	BRAFTOVI with cetuximab N=216		Irinotecan with cetuximab or FOLFIRI with cetuximab N=193	
	All Grades (%)	≥ Grade 3[b] (%)	All Grades (%)	≥ Grade 3 (%)
Dermatitis acneiform[c]	32	1	43	3
Rash[c]	26	0	26	2
Pruritus[c]	14	0	6	0
Melanocytic nevus	14	0	0	0
Dry skin[c]	13	0	12	1
Nervous System Disorders				
Headache[c]	20	0	3	0
Peripheral neuropathy[c]	12	1	6	0
Vascular Disorders				
Hemorrhage[c]	19	2	9	0
Psychiatric Disorders				
Insomnia[c]	13	0	6	0

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Grade 4-5 adverse reactions in the BRAFTOVI with cetuximab arm were limited to Grade 5 hemorrhage (n=1).
[c] c. Represents a composite of multiple, related preferred terms.

Other clinically important adverse reactions occurring in <10% of patients who received BRAFTOVI in combination with cetuximab were:

Gastrointestinal disorders: *Pancreatitis*

Table 10: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Receiving BRAFTOVI in Combination With Cetuximab in BEACON CRC[a]

Laboratory Abnormality[b]	BRAFTOVI with cetuximab		Irinotecan with cetuximab or FOLFIRI with cetuximab	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	34	4	48	5
Lymphopenia	24	7	35	5
Increased Activated Partial Thromboplastin Time	13	1	7	1
Chemistry				
Hypomagnesemia	19	0	22	1
Increased Alkaline Phosphatase	18	4	30	7
Increased ALT	17	0	29	3
Increased AST	15	1	22	2
Hypokalemia	12	3	32	5
Hyponatremia	11	2	13	2

[a] Grades per National Cancer Institute CTCAE v4.03.

Based on the number of patients with available baseline and at least

BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

The safety of BRAFTOVI in combination with binimetinib was evaluated in 98 patients with BRAF V600E mutation-positive metastatic NSCLC who received BRAFTOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in an open-label, single-arm trial (PHAROS).

The PHAROS trial [see Clinical Studies (13.3)] excluded patients with abnormal left ventricular ejection fraction, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of treatment for BRAFTOVI and binimetinib was 9.2 and 8.4 months, respectively.

The most common (≥25%) adverse reactions in patients receiving BRAFTOVI were fatigue, nausea, diarrhea, musculoskeletal pain, vomiting, abdominal pain, visual impairment, constipation, dyspnea, rash, and cough.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 59% of patients receiving BRAFTOVI; the most common (≥5%) were diarrhea (17%); nausea (13%); musculoskeletal pain, fatigue (8% each); AST increased (7%); ALT increased, anemia, hemorrhage, vomiting (6% each); and acute kidney

injury (5%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI; the most common (≥5%) were diarrhea, nausea (8% each); AST increased and fatigue (5% each). A total of 16% of patients receiving BRAFTOVI experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI; the most common (≥2%) were diarrhea, musculoskeletal pain (3.1% each); fatigue, rash, nausea, visual impairment, and vomiting (2% each). None

of the other adverse reactions leading to permanent discontinuation of BRAFTOVI occurred in more than 1 patient.

Serious adverse reactions occurred in 38% of patients who received BRAFTOVI in combination with binimetinib. Serious adverse reactions occurring in ≥2% of patients were hemorrhage (6%); diarrhea (4.1%); anemia, dyspnea, pneumonia (3.1% each); arrhythmia, device related infection, edema, myocardial infarction, and pleural effusion (2% each). Fatal adverse reactions occurred in 2% of patients who received BRAFTOVI (450 mg once daily) in combination with binimetinib, including intracranial hemorrhage and myocardial infarction (1% each).

Table 11 and Table 12 present adverse drug reactions and laboratory abnormalities, respectively, identified in PHAROS.

Table 11: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in PHAROS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=98	
	All Grades (%)	Grades 3 and 4[b] (%)
General Disorders and Administration Site Conditions		
Fatigue[c]	61	8
Edema[d]	23	1
Pyrexia	22	0
Gastrointestinal Disorders		
Nausea	58	3.1
Diarrhea[e]	52	7
Vomiting	37	1
Abdominal pain[f]	32	1
Constipation	27	0
Eye Disorders		
Visual impairment[g]	29	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[h]	48	4.1
Skin and Subcutaneous Tissue Disorders		
Rash[i]	27	3.1
Pruritis[j]	16	0
Dry skin	13	0
Alopecia	12	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea[k]	27	8
Cough[l]	26	0
Nervous System Disorders		
Dizziness[m]	17	1
Headache	11	0
Metabolism and Nutrition Disorders		
Decreased appetite	14	1
Vascular Disorders		
Hemorrhage[b,n]	12	4.1
Hypertension	10	5

Cardiac Disorders		
Left ventricular dysfunction/cardiomyopathy[o]	11	1
Investigations		
Weight increased	11	1
Psychiatric Disorders		
Insomnia	10	0

a. Grades per National Cancer Institute CTCAE v4.03.
b. One Grade 5 adverse reaction of hemorrhage occurred.
c. Fatigue includes fatigue, asthenia.
d. Edema includes edema peripheral, generalized edema, swelling, localized edema, face edema.
e. Diarrhea includes diarrhea, colitis.
f. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort.
g. Visual impairment includes vision blurred, visual impairment, vitreous floaters, photophobia, visual acuity reduced, photopsia.
h. Musculoskeletal pain includes back pain, arthralgia, pain in extremity, myalgia, musculoskeletal chest pain, non-cardiac chest pain, neck pain.
i. Rash includes rash, rash macular, rash maculo-papular, rash papular, rash pustular, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, eczema, skin exfoliation.
j. Pruritis includes pruritus, pruritus genital.
k. Dyspnea includes dyspnea, dyspnea exertional.
l. Cough includes cough, productive cough.
m. Dizziness includes dizziness, balance disorder.
n. Hemorrhage includes anal hemorrhage, hemothorax, gastrointestinal hemorrhage, hematochezia, hematuria, hemoptysis, hemorrhage intracranial, hyphema, small intestinal hemorrhage, upper gastrointestinal hemorrhage, vaginal hemorrhage.
o. Left ventricular dysfunction/cardiomyopathy includes ejection fraction decreased, cardiac failure, cardiac failure congestive.

Other clinically important adverse reactions occurring in <10% of patients who received BRAFTOVI in combination with binimetinib were:

Nervous system disorders: Peripheral neuropathy, Dysgeusia, Facial paresis

Gastrointestinal disorders: Pancreatitis

Skin and subcutaneous tissue disorders: Hyperkeratosis, Erythema, Photosensitivity

Immune system disorders: Drug hypersensitivity

Table 12: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Receiving BRAFTOVI with Binimetinib[a]

Laboratory Abnormality[b]	BRAFTOVI with binimetinib	
	All Grades (%)	Grades 3 and 4 (%)
Hematology		
Anemia	47	11
Lymphopenia	24	6
Thrombocytopenia	20	1.1
Leukopenia	12	0
Neutropenia	12	1.1
Chemistry		
Increased creatinine	91	3.2
Hyperglycemia	48	6
Increased creatine kinase	41	3.3
Lipase increased	40	14
Increased ALT	34	9
Hypoalbuminemia	32	0
Increased AST	31	10
Increased alkaline phosphatase	31	3.2

Hyperkalemia	31	2.1
Hyponatremia	26	11
Serum amylase increased	22	1.1
Hypocalcemia	12	2.1

a. Grades per National Cancer Institute CTCAE v4.03.
b. Based on the number of patients with available baseline and at least one on-treatment laboratory test.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRAFTOVI

Strong or Moderate CYP3A4 Inhibitors

Coadministration of BRAFTOVI with a strong or moderate CYP3A4 inhibitor increases encorafenib plasma concentrations *[see Clinical Pharmacology (11.3)]* and may increase encorafenib adverse reactions. Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the BRAFTOVI dose *[see Dosage and Administration (2.6)]*.

Strong CYP3A4 Inducers

Coadministration of BRAFTOVI with a strong CYP3A4 inducer may decrease encorafenib plasma concentrations *[see Clinical Pharmacology (11.3)]* and may decrease encorafenib efficacy. Avoid coadministration of BRAFTOVI with strong CYP3A4 inducers.

7.2 Effect of BRAFTOVI on Other Drugs

Sensitive CYP3A4 Substrates

BRAFTOVI is a strong CYP3A4 inducer at steady-state. Concomitant use of BRAFTOVI may decrease the plasma concentrations of CYP3A4 substrates (including hormonal contraceptives), *[see Clinical Pharmacology (11.3)]*, which may reduce the efficacy of these substrates. Avoid the coadministration of BRAFTOVI with CYP3A4 substrates for which a decrease in plasma concentration may lead to reduced efficacy of the substrate. If the coadministration cannot be avoided, see the CYP3A4 substrate product labeling for recommendations.

OATP1B1, OATP1B3, or BCRP Substrates

Coadministration of BRAFTOVI with OATP1B1, OATP1B3, or BCRP substrates can result in increased concentrations of the substrates, and may increase toxicity of these agents. When used in combination, monitor patients closely for signs and symptoms of increased exposure and consider adjusting the dose of these substrates *[see Clinical Pharmacology (11.3)]*.

7.3 Drugs That Prolong the QT Interval

BRAFTOVI is associated with dose-dependent QTc interval prolongation *[see Warnings and Precautions (0), Clinical Pharmacology (11.2)]*. Avoid coadministration of BRAFTOVI with drugs known to prolong the QT/QTc interval.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (11.1)]*. There are no available clinical data on the use of BRAFTOVI during pregnancy. In animal reproduction studies, encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the clinical dose of 450 mg, with no clear findings at lower doses *(see Data)*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Data

Animal Data

In reproductive toxicity studies, administration of encorafenib to rats during the period of organogenesis resulted in maternal toxicity, decreased fetal weights, and increased incidence of total skeletal variations at a dose of 20 mg/kg/day (approximately 26 times the human exposure based on area under the concentration-time curve [AUC] at the recommended clinical dose of 450 mg once daily). In pregnant rabbits, administration of encorafenib during the period of organogenesis resulted in maternal toxicity, decreased fetal body weights, increased incidence of total skeletal variations and increased post-implantation loss, including total loss of pregnancy at a dose of 75 mg/kg/day (approximately 178 times the human exposure based on AUC at the recommended clinical dose of 450 mg once daily). While formal placental transfer studies have not been performed, encorafenib exposure in the fetal plasma of both rats and rabbits was up to 1.7% and 0.8%, respectively, of maternal exposure.

8.2 Lactation

Risk Summary

There are no data on the presence of encorafenib or its metabolites in human milk or the effects of encorafenib on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child from BRAFTOVI, advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

BRAFTOVI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating BRAFTOVI *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with BRAFTOVI and for 2 weeks after the last dose. Counsel patients to use a non-hormonal method of contraception since BRAFTOVI has the potential to render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Infertility

Males

Based on findings in male rats at doses approximately 13 times the human exposure at the 450 mg clinical dose, use of BRAFTOVI may impact fertility in males *[see Nonclinical Toxicology (12.1)]*.

8.4 Pediatric Use

The safety and effectiveness of BRAFTOVI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 690 patients with BRAF mutation-positive melanoma who received BRAFTOVI in combination with binimetinib across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older *[see Clinical Studies (13.1)]*.

Of the 231 patients with BRAF V600E mutation-positive metastatic CRC who received BRAFTOVI in combination with cetuximab and mFOLFOX6, 83 (36%) were 65 years of age and over and 16 (7%) were 75 years of age and over [see Clinical Studies (13.2)].

Of the 216 patients with BRAF V600E mutation positive metastatic CRC who received BRAFTOVI in combination with cetuximab, 62 (29%) were 65 years of age to up to 75 years of age, while 20 (9%) were 75 years of age and over *[see Clinical Studies (13.2)]*.

Of the 98 patients with BRAF V600E mutation-positive metastatic NSCLC who received BRAFTOVI with binimetinib, 62 (63%) were 65 years of age and over and 20 (20%) were 75 years and over [see Clinical Studies (13.3)].

8.6 No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib, BRAFTOVI plus cetuximab, or BRAFTOVI plus cetuximab and mFOLFOX6 were observed in older patients as compared to younger patients. Hepatic Impairment

No BRAFTOVI dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (11.3)]*. A recommended dosage has not been established in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

8.7 Renal Impairment

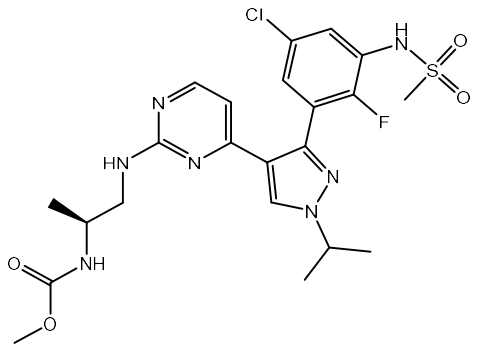
No BRAFTOVI dosage adjustment is recommended in patients with mild to moderate renal impairment (CLcr 30 to < 90 mL/min) *[see Clinical Pharmacology (11.3)]*. A recommended dosage has not been established in patients with severe renal impairment (CLcr <30 mL/min).

9 OVERDOSAGE

Since encorafenib is 86% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with BRAFTOVI.

10 DESCRIPTION

Encorafenib is a kinase inhibitor. The chemical name is methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate. The molecular formula is $C_{22}H_{27}ClFN_7O_4S$ and the molecular weight is 540 daltons. The chemical structure of encorafenib is shown below:



Encorafenib is a white to almost white powder. In aqueous media, encorafenib is slightly soluble at pH 1, very slightly soluble at pH 2, and insoluble at pH 3 and higher.

BRAFTOVI (encorafenib) capsules for oral use contain 75 mg of encorafenib with the following inactive ingredients: copovidone, microcrystalline cellulose, succinic acid, poloxamer 188, crospovidone, colloidal silicon dioxide, magnesium stearate (vegetable origin). The capsule shell contains gelatin, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide, monogramming ink (Pharmaceutical Glaze (Shellac-

45% in Ethanol), Ferrosoferric oxide, N-Butyl Alcohol, Isopropyl Alcohol, Propylene Glycol, Ammonium Hydroxide 28%).

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Encorafenib is a kinase inhibitor that targets BRAF V600E, as well as wild-type BRAF and CRAF in in vitro cell-free assays with IC_{50} values of 0.35, 0.47, and 0.3 nM, respectively. Mutations in the BRAF gene, such as BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Encorafenib was also able to bind to other kinases in vitro including JNK1, JNK2, JNK3, LIMK1, LIMK2, MEK4, and STK36 and reduce ligand binding to these kinases at clinically achievable concentrations (≤0.9 μM).

Encorafenib inhibited in vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. In mice implanted with tumor cells expressing BRAF V600E, encorafenib induced tumor regressions associated with RAF/MEK/ERK pathway suppression.

Encorafenib and binimetinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared with either drug alone, coadministration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in BRAF mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in BRAF V600E mutant human melanoma xenograft studies in mice. Additionally, the combination of encorafenib and binimetinib delayed the emergence of resistance in BRAF V600E mutant human melanoma xenografts in mice compared to either drug alone.

In a BRAF V600E mutant NSCLC patient-derived xenograft model in mice, coadministration of encorafenib and binimetinib resulted in greater anti-tumor activity compared to binimetinib alone, with respect to tumor growth inhibition. Increased tumor growth delay after dosing cessation was also observed with the coadmnistration compared to either drug alone.

In the setting of BRAF-mutant CRC, induction of EGFR-mediated MAPK pathway activation has been identified as a mechanism of resistance to BRAF inhibitors. Combinations of a BRAF inhibitor and agents targeting EGFR have been shown to overcome this resistance mechanism in nonclinical models. Coadministration of encorafenib and cetuximab had an anti-tumor effect greater than either drug alone, in a mouse model of colorectal cancer with mutated BRAF V600E.

11.2 Pharmacodynamics

Cardiac Electrophysiology

A dedicated study to evaluate the QT prolongation potential of BRAFTOVI has not been conducted. BRAFTOVI is associated with dose-dependent QTc interval prolongation. Based on a central tendency analysis of QTc in a study of adult patients with melanoma who received the recommended dose of BRAFTOVI in combination with binimetinib, the largest mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (14 to 22) ms *[see Warnings and Precautions (0)]*.

11.3 Pharmacokinetics

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or V600K mutation and BRAF V600E mutation-positive metastatic CRC. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg (0.1 to 1.6 times the maximum recommended dose of 450 mg). After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 mg (0.1 to 1.8 times the maximum recommended dose of 450 mg). Steady-state was reached within 15 days, with exposure being 50% lower compared to Day 1; intersubject variability (CV%) of AUC ranged from 12% to 69%.

Absorption

The median T_{max} of encorafenib is 2 hours. At least 86% of the dose is absorbed.

Effect of Food

Following administration of a single dose of BRAFTOVI 100 mg (0.2 times the maximum recommended dose of 450 mg) with a high-fat, high-calorie meal (consisting of approximately 150 calories from protein, 350 calories from carbohydrates, and 500 calories from fat) the mean maximum encorafenib concentration (C_{max}) decreased by 36% and there was no effect on AUC.

Distribution

The geometric mean (CV%) of apparent volume of distribution is 164 L (70%). The protein binding of encorafenib is 86% in vitro. The blood-to-plasma concentration ratio is 0.58.

Elimination

The mean (CV%) terminal half-life ($t_{1/2}$) of encorafenib is 3.5 hours (17%), and the apparent clearance is 14 L/h (54%) at day 1, increasing to 32 L/h (59%) at steady-state at the maximum recommended dose of 450 mg.

Metabolism

Encorafenib is primarily metabolized by CYP3A4 (83%) and to a lesser extent by CYP2C19 (16%) and CYP2D6 (1%).

Excretion

Following a single radiolabeled dose of 100 mg encorafenib, 47% (5% unchanged) of the administered dose was recovered in feces and 47% (2% unchanged) in urine.

Specific Populations

No clinically significant differences in the pharmacokinetics of encorafenib were observed based on age (19 to 94 years), sex, body weight (34 to 168 kg), mild hepatic impairment (Child-Pugh Class A), and mild or moderate renal impairment (CLcr 30 to < 90 mL/min). The effect of race or ethnicity, moderate or severe hepatic impairment (Child-Pugh Class B or C), and severe renal impairment (CLcr <30 mL/min) on encorafenib pharmacokinetics have not been studied.

Drug Interaction Studies

Clinical Studies

CYP3A4 Inhibitors: Coadministration of posaconazole (strong CYP3A4 inhibitor) or diltiazem (moderate CYP3A4 inhibitor) increased AUC of encorafenib by 3- and 2-fold, respectively, and increased C_{max} by 68% and 45%, respectively, after a single dose of 50 mg BRAFTOVI (0.1 times the maximum recommended dose of 450 mg).

Strong CYP3A4 Inducers: The effect of a strong CYP3A4 inducer on encorafenib exposure has not been studied *[see Drug Interactions (7.1)]*.

Moderate CYP3A4 Inducers: Repeat dose administration of BRAFTOVI 450 mg once daily and binimetinib 45 mg twice daily with modafinil, a moderate CYP3A4 inducer, decreased encorafenib steady-state AUC by 24% and C_{max} by 20%, compared to BRAFTOVI alone.

Effect of encorafenib on CYP3A4 Substrates: Repeat dose administration of BRAFTOVI 450 mg once daily and binimetinib 45 mg twice daily with a single dose of midazolam 2 mg, a sensitive CYP3A4 substrate, decreased midazolam AUC by 82% and C_{max} by 74% relative to midazolam 2 mg alone.

Effect of encorafenib on Other CYP Substrates: There was no clinically significant effect of repeat dose administration of BRAFTOVI 450 mg once daily and binimetinib 45 mg twice daily on the exposure of substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP2D6.

Proton Pump Inhibitors: No clinically significant differences in encorafenib pharmacokinetics were observed when coadministered with rabeprazole.

Binimetinib: No clinically significant differences in the pharmacokinetics of binimetinib (UGT1A1 substrate) were observed when coadministered with BRAFTOVI (UGT1A1 inhibitor).

Cetuximab: No clinically significant differences in the pharmacokinetics of encorafenib or cetuximab were observed when the recommended BRAFTOVI dose of 300 mg was coadministered with cetuximab.

Transporters: Repeat dose administration of BRAFTOVI 450 mg once daily and binimetinib 45 mg twice daily with a single dose of rosuvastatin (a sensitive substrate for OATP1B1, OATP1B3, and BCRP) increased rosuvastatin Cmax by 2.7-fold and AUC by 1.6-fold.

In Vitro Studies

CYP/UGT Enzymes: Encorafenib is a reversible inhibitor of UGT1A1.

Transporters: Encorafenib is a substrate of P-glycoprotein (P-gp) but not of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide (OATP1B1, OATP1B3) or organic cation transporter (OCT1) at clinically relevant plasma concentrations.

Encorafenib is an inhibitor of P-gp, BCRP, OCT2, organic anion transporter (OAT1, OAT3), OATP1B1, and OATP1B3, but not of OCT1 or MRP2 at clinically relevant plasma concentrations.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with encorafenib have not been conducted. Encorafenib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, or micronuclei in bone marrow of rats.

No dedicated fertility studies were performed with encorafenib in animals. In a general toxicology study in rats, decreased testes and epididymis weights, tubular degeneration in testes, and oligospermia in epididymides were observed at doses approximately 13 times the human exposure at the 450 mg clinical dose based on AUC. No effects on reproductive organs were observed in either sex in any of the non-human primate toxicity studies.

12.2 Animal Toxicology and/or Pharmacology

Adverse histopathology findings of hyperplasia and hyperkeratosis occurred in the stomach of rats at encorafenib doses of 20 mg/kg/day (approximately 14 times the human exposure at the 450 mg clinical dose based on AUC) or greater, in both 4 and 13-week studies.

13 CLINICAL STUDIES

13.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

BRAFTOVI in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Randomization was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and prior immunotherapy for unresectable or metastatic disease (yes versus no).

Patients were randomized (1:1:1) to receive BRAFTOVI 450 mg once daily in combination with binimetinib 45 mg twice daily (BRAFTOVI in combination with binimetinib), BRAFTOVI 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved dosing (BRAFTOVI 450 mg in combination with binimetinib 45 mg) are described below.

The major efficacy outcome measure was progression-free survival (PFS), as assessed by a blinded independent central review, to compare BRAFTOVI in combination with binimetinib with vemurafenib. Additional efficacy outcome measures included overall survival (OS), as well as objective response rate (ORR) and duration of response (DoR) which were assessed by central review.

A total of 577 patients were randomized, 192 to the BRAFTOVI in combination with binimetinib arm, 194 to the BRAFTOVI arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the BRAFTOVI in combination with binimetinib or the vemurafenib arms, the median age was 56 years (20 to 89 years), 59% were male, 91% were White, and 72% had baseline ECOG performance status of 0. Ninety-five percent (95%) had metastatic disease, 65% were Stage IVM1c, and 4% received prior CTLA-4, PD-1, or PD-L1 directed antibodies. Twenty-eight percent (28%) had elevated baseline serum lactate dehydrogenase (LDH), 45% had ≥ 3 organs with tumor involvement at baseline, and 3% had brain metastases. Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%).

BRAFTOVI in combination with binimetinib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 13 and Figure 1.

Table 13: Efficacy Results for COLUMBUS

	BRAFTOVI with binimetinib N=192	**Vemurafenib N=191**
Progression-Free Survival		
Number of events (%)	98 (51)	106 (55)
Progressive disease	88 (46)	104 (54)
Death	10 (5)	2 (1)
Median PFS, months (95% CI)	14.9 (11.0, 18.5)	7.3 (5.6, 8.2)
HR (95% CI)[a]	0.54 (0.41, 0.71)	
P-value[b]	<0.0001	
Overall Survival[c]		
Number of events (%)	139 (72)	147 (77)
Median OS, months (95% CI)	33.6 (24.4, 39.2)	16.9 (14.0, 24.5)
HR (95% CI)[a]	0.67 (0.53, 0.84)	
Overall Response Rate		
ORR (95% CI)	63% (56%, 70%)	40% (33%, 48%)
CR	8%	6%
PR	55%	35%
Duration of Response		
Median DoR, months (95% CI)	16.6 (12.2, 20.4)	12.3 (6.9, 16.9)

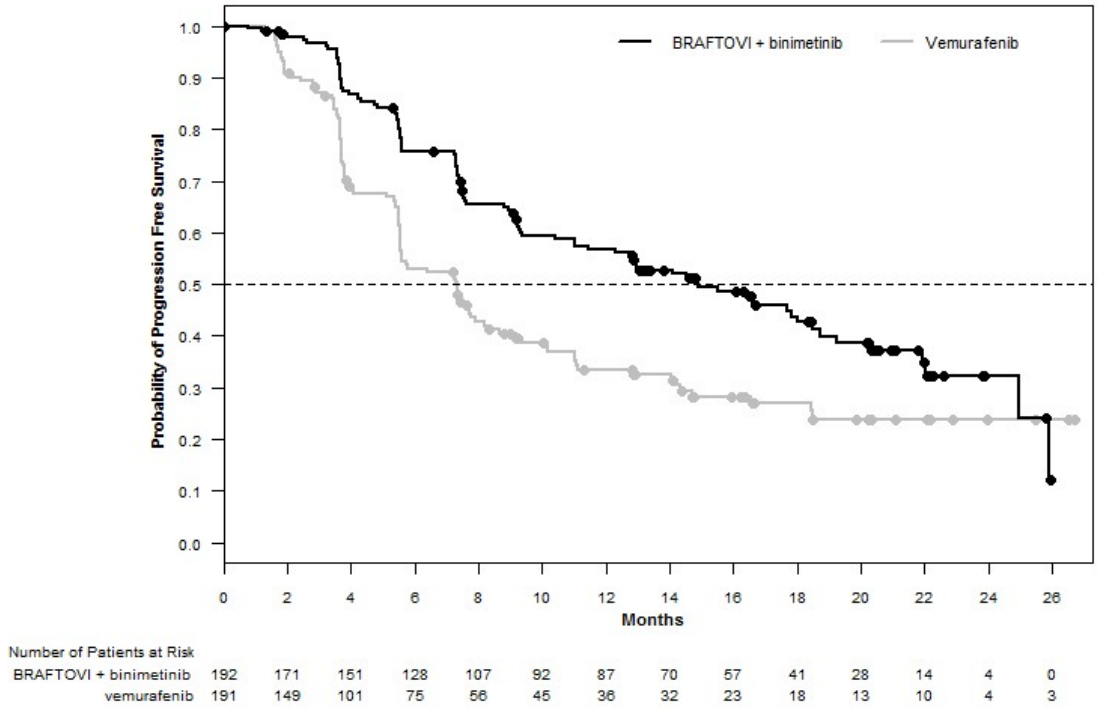
CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response.

[a] Estimated with Cox proportional hazard model adjusted by the following stratification factors: American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

[b] Log-rank test adjusted by the same stratification factors.

[c] Based on a cutoff date of 82.4 months after the date of the PFS analysis.

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in COLUMBUS



13.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (mCRC)-BRAFTOVI with Cetuximab and mFOLFOX6

BRAFTOVI in combination with cetuximab and mFOLFOX6 was evaluated in a randomized, active-controlled, open-label, multicenter trial (BREAKWATER CRC; NCT04607421). Eligible patients were required to have BRAF V600E mutation-positive metastatic colorectal cancer (CRC), as detected using the Qiagen therascreen BRAF V600E RGQ polymerase chain reaction (PCR) Kit. Other key eligibility criteria included no prior systemic treatment in the metastatic setting, absence of prior treatment with any selective BRAF inhibitor or EGFR inhibitor, tumor that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) unless the patient is ineligible to receive immune checkpoint inhibitors, tumor that is not RAS-mutated or for which RAS mutation status is unknown, and Eastern Cooperative Oncology Group (ECOG) performance status 0-1. Randomization was stratified by ECOG performance status (0 versus 1) and region (US/Canada versus Europe versus Rest of World).

Patients were initially randomized 1:1:1 to one of the following treatment arms, and then 1:1 after discontinuation of enrollment of the BRAFTOVI+cetuximab arm (158 patients):

• BRAFTOVI 300 mg orally once daily in combination with cetuximab 500 mg/m2 IV infusion every 2 weeks (BRAFTOVI+cetuximab arm)

• BRAFTOVI 300 mg orally once daily in combination with cetuximab 500 mg/m2 IV infusion every 2 weeks and mFOLFOX6 every 2 weeks (BRAFTOVI+cetuximab+mFOLFOX6 arm)

• mFOLFOX6 (every 2 weeks), or FOLFOXIRI (every 2 weeks), or CAPOX (every 3 weeks), each with or without bevacizumab (administered per prescribing instructions)

mFOLFOX6 consisted of oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, 5-FU 400 mg/m2 IV bolus, then 5-FU 2400 mg/m2 continuous IV infusion over 46-48 hours; CAPOX consisted of oxaliplatin 130 mg/m2 IV infusion 27 Reference ID: 5548023and capecitabine 1000 mg/m2 oral tablet twice daily on Days 1-14; FOLFOXIRI consisted of irinotecan 165 mg/m2, oxaliplatin 85 mg/m2,

leucovorin 400 mg/m2, 5-FU 2400 or 3200 mg/m2 (per local standard of care) continuous IV infusion over 46-48 hours.

Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, lost to follow-up, or death. Only the results of the approved regimen (BRAFTOVI in combination with cetuximab and mFOLFOX6) are described below.

The major efficacy outcome measure was confirmed objective response rate (ORR) as assessed by BICR and was evaluated in the first 110 participants randomized in each arm. An additional efficacy outcome measure included duration of response (DoR) as assessed by BICR.

A total of 236 patients were randomized to the BRAFTOVI+cetuximab+mFOLFOX6 arm and 243 to the control arm. Of these patients, the median age was 61 years, 50% were female, 60% were White, 37% were Asian, 0.4% were Multiracial, 0.2% were Black or African American, and 2.5% were not reported. Twelve percent (12%) were Hispanic or Latino, 81% were not Hispanic or Latino, and 7% were not reported. Fifty-four percent (54%) had baseline ECOG performance status of 0.

BRAFTOVI in combination with cetuximab and mFOLFOX6 demonstrated a statistically significant improvement in ORR compared to the active comparator. Efficacy results are summarized in Table 14 below.

Table 14: Efficacy Results for BREAKWATER

Efficacy Parameter	BRAFTOVI with cetuximab and mFOLFOX6 N=110	mFOLFOX6 ± bevacizumab or FOLFOXIRI ± bevacizumab or CAPOX ± bevacizumab N=110
Objective Response Rate (per BICR)		
ORR (95% CI)	61% (52%, 70%)	40% (31%, 49%)
CR	2.7%	1.8%
PR	58%	38%
P-value[a]	0.0008	
Duration of Response (per BICR)		
Median DoR, months (95% CI)	13.9 (8.5, NE)	11.1 (6.7, 12.7)
% with DoR ≥6 months	69%	34%
% with DoR ≥12 months	22%	11%

CI = Confidence interval; CR = Complete response; DoR = Duration of response; N = Number of patients; NE = Not estimable; ORR = Objective response rate; PR = Partial response.

a. Stratified by ECOG performance status and geographic region at randomization. Cochran-Mantel-Haenszel test; tested at 1-sided alpha level of 0.001.

13.3 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

BRAFTOVI in combination with cetuximab was evaluated in a randomized, active-controlled, open-label, multicenter trial (BEACON CRC; NCT02928224). Eligible patients were required to have BRAF V600E mutation-positive metastatic colorectal cancer (CRC), as detected using the Qiagen therascreen BRAF V600E RGQ polymerase chain reaction (PCR) Kit, with disease progression after 1 or 2 prior regimens. Other key eligibility criteria included absence of prior treatment with a RAF, MEK, or EGFR inhibitor, eligibility to receive cetuximab per local labeling with respect to tumor RAS status, and ECOG performance status (PS) 0-1. Randomization was stratified by Eastern Cooperative Oncology Group (ECOG)

performance status (0 versus 1), prior use of irinotecan (yes versus no), and cetuximab product used (US-licensed versus EU-approved).

Patients were randomized 1:1:1 to one of the following treatment arms:

- BRAFTOVI 300 mg orally once daily in combination with cetuximab (BRAFTOVI/cetuximab arm)
- BRAFTOVI 300 mg orally once daily in combination with binimetinib and cetuximab
- Irinotecan with cetuximab or FOLFIRI with cetuximab (control arm)

The dosage of cetuximab in all patients was 400 mg/m^2 intravenously for the first dose followed by 250 mg/m^2 weekly.

Patients in the control arm received cetuximab with either irinotecan 180 mg/m^2 intravenously on Days 1 and 15 of each 28-day cycle or FOLFIRI intravenously (irinotecan 180 mg/m^2 on Days 1 and 15; folinic acid 400 mg/m^2 on Days 1 and 15; then fluorouracil 400 mg/m^2 bolus on Days 1 and 15 followed by fluorouracil 2400 mg/m^2/day by continuous infusion over 2 days).

Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved regimen (BRAFTOVI in combination with cetuximab) are described below.

The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures included progression-free survival (PFS), overall response rate (ORR), and duration of response (DoR) as assessed by blinded independent central review (BICR). OS and PFS were assessed in all randomized patients. ORR and DoR were assessed in the subset of the first 220 patients included in the randomized portion of the BRAFTOVI/cetuximab and control arm of the study.

A total of 220 patients were randomized to the BRAFTOVI/cetuximab arm and 221 to the control arm. Of these 441 patients, the median age was 61 years; 53% were female; 80% were White and 15% were Asian. Fifty percent (50%) had baseline ECOG performance status of 0; 66% received 1 prior therapy and 34% received 2; 93% received prior oxaliplatin and 52% received prior irinotecan.

BRAFTOVI in combination with cetuximab demonstrated a statistically significant improvement in OS, ORR, and PFS compared to the active comparator. Efficacy results are summarized in Table and Figure 2.

Table 15: Efficacy Results From BEACON CRC

	BRAFTOVI with cetuximab N = 220	**Irinotecan with cetuximab or FOLFIRI with cetuximab N = 221**
Overall Survival		
Number of Events (%)	93 (42)	114 (52)
Median OS, months (95% CI)	8.4 (7.5, 11.0)	5.4 (4.8, 6.6)
HR (95% CI)[a,b]	0.60 (0.45, 0.79)	
P-value[a,c]	0.0003	
Overall Response Rate (per BICR)		
ORR (95% CI)[d]	20% (13%, 29%)	2% (0%, 7%)
CR	5%	0%
PR	15%	2%
P-value[a,e]	<0.0001	
Median DoR, months (95% CI)	6.1 (4.1, 8.3)	NR (2.6, NR)
Progression Free Survival (per BICR)		
Number of events (%)	133 (60)	128 (58)
Progressive disease	110 (50)	101 (46)
Death	23 (10)	27 (12)
Median PFS, months (95% CI)	4.2 (3.7, 5.4)	1.5 (1.4, 1.7)
HR (95% CI)[a,b]	0.40 (0.31, 0.52)	
P-value[a,f]	< 0.0001	

CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NR = Not reached; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response.

[a] Stratified by ECOG PS, source of cetuximab (US-licensed versus EU-approved) and prior irinotecan use at randomization.

[b] Stratified Cox proportional hazard model.

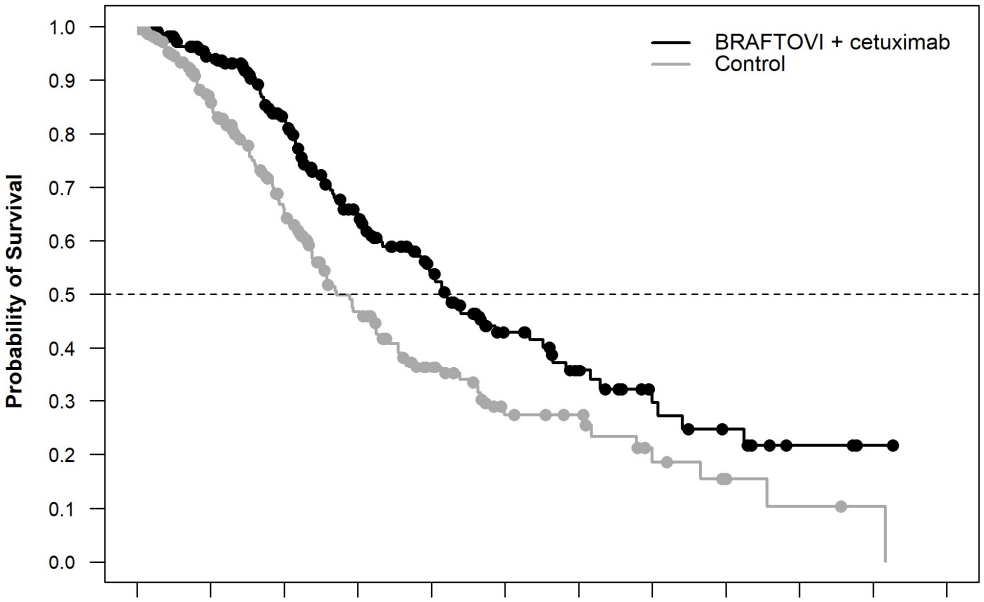
[c] Stratified log-rank test, tested at alpha level of 0.0084.

[d] BRAFTOVI/cetuximab arm (n=113) and control arm (n=107).

[e] Cochran-Mantel-Haenszel test; tested at alpha level of 0.05.

[f] Stratified log-rank test, tested at alpha level of 0.0234.

Figure 2: Kaplan-Meier Curves for Overall Survival in BEACON CRC



Number of Patients at Risk												
BRAFTOVI + cetuximab	220	184	133	87	57	33	21	12	8	3	1	0
Control	221	158	102	60	34	18	15	7	4	2	1	0

13.4 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer

BRAFTOVI in combination with binimetinib was evaluated in an open-label, multicenter, single-arm study in patients with BRAF V600E mutation-positive metastatic non-small cell lung cancer (NSCLC) (PHAROS; NCT03915951). Eligible patients had a diagnosis of histologically-confirmed metastatic NSCLC with BRAF V600E mutation that was treatment-naïve or had been previously treated with 1 prior line of systemic therapy in the metastatic setting (platinum-based chemotherapy and/or anti-PD-1/PD-L1 therapies), age 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Prior use of BRAF inhibitors or MEK inhibitors was not allowed.

Patients received BRAFTOVI 450 mg once daily and binimetinib 45 mg orally twice daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were objective response rate (ORR) per RECIST v1.1 and duration of response (DoR) as assessed by independent review committee (IRC).

In the efficacy population, BRAF V600E mutation status was determined by prospective local testing using tumor tissue (78%) or blood (22%) specimens. Of the 98 patients with BRAF V600E mutation, 6 patients were enrolled into the trial based on testing of their tumor tissue specimens with the FoundationOne CDx tissue test. Of the remaining 92 patients enrolled based on local testing, 68 patients had their tumor tissue specimens retrospectively confirmed as having BRAF V600E positive status by the FoundationOne CDx tissue test. The remaining patients had either BRAF V600E negative status (n=5) or had unevaluable results (n=19) by the FoundationOne CDx tissue test. In addition, plasma samples from 81 out of 98 patients were retrospectively tested using the FoundationOne Liquid CDx assay. Of the 81 patients, 48 were confirmed positive for BRAF V600E, while 33 patients were BRAF V600E mutation negative by FoundationOne Liquid CDx assay. The remaining 17 samples had unevaluable results with FoundationOne Liquid CDx assay.

The efficacy population included 59 treatment-naïve patients and 39 previously-treated patients. Among these 98 patients, the median age was 70 years (range: 47 to 86); 53% female; 88% White, 7% Asian, 3% Black or

African American, and 1% American Indian or Alaska Native; 99% were not Hispanic or Latino; 13% were current smokers and 57% were former smokers; 73% had ECOG PS of 1; and 97% had adenocarcinoma. All patients had metastatic disease, and 8% had brain metastases at baseline.

Efficacy results for patients with BRAF V600E mutation-positive metastatic NSCLC are summarized in Table 13.

Table 16: Efficacy Results for PHAROS

	BRAFTOVI with binimetinib	
Efficacy Parameter	**Treatment naïve (N=59)**	**Previously treated (N=39)**
Objective Response Rate[a]		
ORR (95% CI)	75% (62, 85)	46% (30, 63)
CR	15%	10%
PR	59%	36%
Duration of Response[a]	N=44	N=18
Median DoR, months (95% CI)	NE (23.1, NE)	16.7 (7.4, NE)
% with DoR ≥6 months	75%	67%
% with DoR ≥12 months	59%	33%

CI = Confidence interval; CR = Complete response; DoR = Duration of response; N = Number of patients; NE = Not estimable; ORR = Objective response rate; PR = Partial response.

a. Assessed by Independent Central Review (ICR).

14 HOW SUPPLIED/STORAGE AND HANDLING

BRAFTOVI (encorafenib) is supplied as 75 mg hard gelatin capsules.

75 mg: size OO with a flesh colored opaque cap and a white opaque body, printed with a stylized "A" on the cap and "LGX 75mg" on the body, available in cartons containing two bottles of 90 capsules each.

Store below 25°C.

After first opening: Use within 45 days and store below 25°C.

The expiry date of the product is indicated on the packaging materials.

15 MANUFACTURER

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