THERAPY MANAGEMENT GUIDE

A resource to help support your patients with metastatic non-small cell lung cancer (NSCLC) with a *BRAF V600E* mutation[1]

START | **MONITOR** | **MODIFY**

INDICATION AND USAGE

BRAFTOVI and MEKTOVI are kinase inhibitors indicated for use in combination for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a *BRAF V600E* mutation, as detected by an FDA-approved test.

Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF NSCLC.

IMPORTANT SAFETY INFORMATION

The information below applies to the safety of the combination of BRAFTOVI and MEKTOVI unless otherwise noted. See full Prescribing Information for BRAFTOVI and for MEKTOVI for dose modifications for adverse reactions.

WARNINGS AND PRECAUTIONS

New Primary Malignancies: New primary malignancies, cutaneous and non-cutaneous, can occur. In the PHAROS trial, cutaneous squamous cell carcinoma (cuSCC) and skin papilloma (SP), each occurred in 2% of patients. 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. Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies. Monitor patients for new malignancies prior to initiation of treatment, while on treatment, and after discontinuation of treatment.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

BRAF, B-Raf proto-oncogene.

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

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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 exposed to BRAF inhibitors. Confirm evidence of *BRAF V600E* or *V600K* mutation using an FDA-approved test prior to initiating BRAFTOVI.

Cardiomyopathy: Cardiomyopathy manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. In the PHAROS trial, evidence of cardiomyopathy occurred in 11% and Grade 3 left ventricular dysfunction occurred in 1% of patients. Cardiomyopathy resolved in 82% of patients. Assess left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated acquisition (MUGA) scan prior to initiating treatment, 1 month after initiating treatment, and then every 2 to 3 months during treatment. The safety has not been established in patients with a 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hepatotoxicity: Hepatotoxicity can occur when MEKTOVI is administered in combination with BRAFTOVI. In the PHAROS trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests was 10% for aspartate aminotransferase (AST), 9% for alanine aminotransferase (ALT), and 3.2% for alkaline phosphatase. Monitor liver laboratory tests before initiation of BRAFTOVI and MEKTOVI, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Rhabdomyolysis: Rhabdomyolysis can occur when MEKTOVI is administered in combination with BRAFTOVI. In the PHAROS trial, elevation of laboratory values of serum creatine kinase (CK) occurred in 41% of patients. No patient experienced rhabdomyolysis. Monitor CPK and creatinine levels prior to initiating MEKTOVI, periodically during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hemorrhage: Hemorrhage can occur when BRAFTOVI is administered in combination with MEKTOVI. In the PHAROS trial, hemorrhage occurred in 12% of patients, including a fatal intracranial hemorrhage (1%); Grade 3 or 4 hemorrhage occurred in 4.1% of patients. The most frequent hemorrhagic events were anal hemorrhage and hemothorax (2% each). Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Venous Thromboembolism (VTE): In the PHAROS trial, VTE occurred in 7% of patients, including 1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Ocular Toxicities: In the PHAROS trial, serous retinopathy (retinal detachment) occurred in 2% of patients with no cases of blindness. Retinal vein occlusion (RVO) is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with MEKTOVI in combination with BRAFTOVI. The safety of MEKTOVI has not been established in patients with a history of RVO or current risk factors for RVO including uncontrolled glaucoma or a history of hyperviscosity or hypercoagulability syndromes. Perform ophthalmological evaluation for patient-reported acute vision loss or other visual disturbance within 24 hours. Permanently discontinue MEKTOVI in patients with documented RVO. Uveitis, including iritis and iridocyclitis, was reported in patients treated with MEKTOVI in combination with BRAFTOVI. In PHAROS, uveitis occurred in 1% of patients. Assess for visual symptoms at each visit. Perform an ophthalmological 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.

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

IMPORTANT SAFETY INFORMATION (cont)

QT Prolongation: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the PHAROS trial, an increase in QTcF to >500 ms was measured in 2.1% (2/95) of patients who received BRAFTOVI with MEKTOVI. 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.

Interstitial Lung Disease (ILD): In the PHAROS trial, 1 patient (1%) receiving MEKTOVI with BRAFTOVI developed pneumonitis. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Embryo-Fetal Toxicity: BRAFTOVI and MEKTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Effective, non-hormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI with MEKTOVI.

Risks Associated with BRAFTOVI as a Single Agent: There is an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with MEKTOVI. If MEKTOVI is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended.

Risks Associated with Combination Treatment: BRAFTOVI is indicated for use as part of a regimen in combination with MEKTOVI. Refer to the prescribing information for BRAFTOVI and MEKTOVI for additional risk information.

Lactation: Advise women not to breastfeed during treatment with BRAFTOVI and MEKTOVI and for 2 weeks after the final dose.

Infertility: Advise males of reproductive potential that BRAFTOVI may impair fertility.

ADVERSE REACTIONS

The most common adverse reactions (≥25%, all grades, in the PHAROS trial) for BRAFTOVI with MEKTOVI were: fatigue (61%), nausea (58%), diarrhea (52%), musculoskeletal pain (48%), vomiting (37%), abdominal pain (32%), visual impairment (29%), constipation (27%), dyspnea (27%), rash (27%), and cough (26%).

Serious adverse reactions occurred in 38% of patients receiving BRAFTOVI with MEKTOVI. Serious adverse reactions (≥2% of patients in the PHAROS trial) were hemorrhage (6%), diarrhea (4.1%), anemia (3.1%), dyspnea (3.1%), pneumonia (3.1%), arrhythmia (2%), device related infection (2%), edema (2%), myocardial infarction (2%), and pleural effusion (2%). Fatal adverse reactions occurred in 2% of patients, including intracranial hemorrhage (1%) and myocardial infarction (1%).

Other clinically important adverse reactions occurring in <10% of patients who received BRAFTOVI with MEKTOVI in the PHAROS trial were peripheral neuropathy, dysgeusia, facial paresis, pancreatitis, hyperkeratosis, erythema, photosensitivity, and drug hypersensitivity.

In the PHAROS trial, the most common laboratory abnormalities (all grades) (≥20%) for BRAFTOVI and MEKTOVI included increased creatinine (91%), hyperglycemia (48%), anemia (47%), increased creatine kinase (41%), lipase increased (40%), increased ALT (34%), hypoalbuminemia (32%), increased alkaline phosphatase (31%), increased AST (31%), hyperkalemia (31%), hyponatremia (26%), lymphopenia (24%), serum amylase increased (22%), and thrombocytopenia (20%).

DRUG INTERACTIONS

Strong or moderate CYP3A4 inhibitors: Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the BRAFTOVI dose.

Strong CYP3A4 inducers: Avoid coadministration of BRAFTOVI with strong CYP3A4 inducers.

Sensitive CYP3A4 substrates: Avoid the coadministration of BRAFTOVI with CYP3A4 substrates (including hormonal contraceptives) 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.

Dose reductions of drugs that are **substrates of OATP1B1, OATP1B3, or BCRP** may be required when used concomitantly with BRAFTOVI.

Avoid coadministration of BRAFTOVI with **drugs known to prolong QT/QTc interval.**

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

Dosing and drug interactions[1,2]

Recommended dose

BRAFTOVI® (encorafenib) 450 mg orally once daily + MEKTOVI® (binimetinib) 45 mg orally twice daily is an approved treatment for adult patients with metastatic non-small cell lung cancer with a *BRAF V600E* mutation[1,2]

Confirm the presence of *BRAF V600E* mutation by an FDA-approved test.[1,2]

Recommended dose

BRAFTOVI 450 mg orally once daily + MEKTOVI 45 mg orally twice daily[1,2]

BRAFTOVI
450 mg

\+

MEKTOVI
45 mg

Six 75 mg BRAFTOVI capsules and three 15 mg MEKTOVI tablets

1st dose

MEKTOVI
45 mg

Three 15 mg MEKTOVI tablets

2nd dose

Treatment with BRAFTOVI + MEKTOVI should be continued until disease progression or unacceptable toxicity[1,2]

- BRAFTOVI may be taken in the morning or evening. Consider each patient's specific needs when discussing recommended administration[1]
- For patients with moderate or severe hepatic impairment, the recommended dose of MEKTOVI is 30 mg orally taken twice daily[2]
- Instruct patients not to take a missed dose of[1,2]
  - BRAFTOVI within **12 hours** of the next dose
  - MEKTOVI within **6 hours** of the next dose
- In case of vomiting, do not take an additional dose of BRAFTOVI + MEKTOVI; resume dosing with the next scheduled dose[1,2]

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

Dosing and drug interactions (cont)[1,2]

A BRAF + MEK inhibitor combination with continuous dosing and no fasting or refrigeration requirements[1,2]

- May be taken with or without food
- No refrigeration requirement
- Continuous dosing

Store BRAFTOVI + MEKTOVI at room temperature.[1,2]

Selected BRAFTOVI drug interactions[1]

Strong or moderate CYP3A4 inhibitors	Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the BRAFTOVI dose. Refer to table below.
Strong CYP3A4 inducers	Avoid coadministration of BRAFTOVI with strong CYP3A4 inducers.
Sensitive CYP3A4 substrates	Avoid the coadministration of BRAFTOVI with CYP3A4 substrates (including hormonal contraceptives) 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	Dose reductions of drugs that are substrates of OATP1B1, OATP1B3, or BCRP may be required when used concomitantly with BRAFTOVI. Monitor patients closely for signs and symptoms of increased exposure.
Drugs known to prolong QT/QTc interval	Avoid coadministration.

Please see full Prescribing Information for BRAFTOVI for more information about drug interactions.

Recommended BRAFTOVI dose reduction when coadministered with a moderate or strong CYP3A4 inhibitor[1]

Current daily dose*	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†

*Current daily dose refers to recommended dose of BRAFTOVI based on indication or reductions for adverse reactions based on dosing recommendations.

†Encorafenib exposure at the 75 mg once daily BRAFTOVI dosage when coadministered with a strong CYP3A4 inhibitor is expected to be higher than at the 150 mg once daily dosage in the absence of a CYP3A4 inhibitor and similar to exposure at the 225 mg once daily 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.

BCRP, breast cancer resistance protein; CYP3A4, cytochrome P450 3A4; MEK, mitogen-activated extracellular signal-regulated kinase; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3.

See recommended dose adjustments for adverse reactions starting on **page 11**.

Select safety profile from the PHAROS trial[1,2]

- **The Use of BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib) is associated with the following WARNINGS and PRECAUTIONS: New Primary Malignancies, Tumor Promotion in BRAF Wild-Type Tumors, Cardiomyopathy, Hepatotoxicity, Rhabdomyolysis, Hemorrhage, Venous Thromboembolism, Ocular Toxicities, QT Prolongation, Interstitial Lung Disease, Embryo-Fetal Toxicity, Risks Associated with BRAFTOVI as a Single Agent, and Risks Associated with Combination Treatment**
- **The most common ARs (≥25%)** were fatigue (61%), nausea (58%), diarrhea (52%), musculoskeletal pain (48%), vomiting (37%), abdominal pain (32%), visual impairment (29%), constipation (27%), dyspnea (27%), rash (27%), and cough (26%)

ARs occurring in ≥10% of patients receiving BRAFTOVI + MEKTOVI*

	BRAFTOVI + MEKTOVI (N=98)	
AR	**All Grades**	**Grades 3/4†**
Fatigue‡	61%	8%
Nausea	58%	3.1%
Diarrhea‡	52%	7%
Musculoskeletal pain‡	48%	4.1%
Vomiting	37%	1%
Abdominal pain‡	32%	1%
Visual impairment‡	29%	2%
Constipation	27%	0%
Dyspnea‡	27%	8%
Rash‡	27%	3.1%
Cough‡	26%	0%
Edema‡	23%	1%

	BRAFTOVI + MEKTOVI (N=98)	
AR continued	**All Grades**	**Grades 3/4†**
Pyrexia	22%	0%
Dizziness‡	17%	1%
Pruritus‡	16%	0%
Decreased appetite	14%	1%
Dry skin	13%	0%
Alopecia	12%	0%
Hemorrhage†‡	12%	4.1%
Headache	11%	0%
Left ventricular dysfuncton/cardiomyopathy‡	11%	1%
Weight increased	11%	1%
Hypertension	10%	5%
Insomnia	10%	0%

- Other clinically important ARs occurring in <10% of patients who received BRAFTOVI + MEKTOVI were peripheral neuropathy, dysgeusia, facial paresis, pancreatitis, hyperkeratosis, erythema, photosensitivity, and drug hypersensitivity

*Grades per National Cancer Institute CTCAE v4.03.

†1 Grade 5 AR of hemorrhage occurred.

‡Fatigue includes fatigue, asthenia; edema includes edema peripheral, generalized edema, swelling, localized edema, face edema; diarrhea includes diarrhea, colitis; abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort; visual impairment includes vision blurred, visual impairment, vitreous floaters, photophobia, visual acuity reduced, photopsia; musculoskeletal pain includes back pain, arthralgia, pain in extremity, myalgia, musculoskeletal chest pain, non-cardiac chest pain, neck pain; rash includes rash, rash macular, rash maculo-papular, rash papular, rash pustular, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, eczema, skin exfoliation; pruritus includes pruritus, pruritus genital; dyspnea includes dyspnea, dyspnea exertional; cough includes cough, productive cough; dizziness includes dizziness, balance disorder; hemorrhage includes anal hemorrhage, hemothorax, gastrointestinal hemorrhage, hematochezia, hematuria, hemoptysis, hemorrhage intracranial, hyphema, small intestinal hemorrhage, upper gastrointestinal hemorrhage, vaginal hemorrhage; left ventricular dysfunction/cardiomyopathy includes ejection fraction decreased, cardiac failure, cardiac failure congestive.

AR, adverse reaction; CTCAE, Common Terminology Criteria for Adverse Events.

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

Select safety profile from the PHAROS trial (cont)[1,2]

Serious and fatal ARs

- **Serious ARs** occurred in 38% of patients who received BRAFTOVI + MEKTOVI. Serious ARs occurring in ≥2% of patients were hemorrhage (6%), diarrhea (4.1%), anemia (3.1%), dyspnea (3.1%), pneumonia (3.1%), arrhythmia (2%), device related infection (2%), edema (2%), myocardial infarction (2%), and pleural effusion (2%)
- **Fatal ARs** occurred in 2% of patients who received BRAFTOVI + MEKTOVI, including intracranial hemorrhage (1%) and myocardial infarction (1%)

ARs leading to dose interruptions, dose reductions, or permanent discontinuation of BRAFTOVI or MEKTOVI

		Overall rate	Most common ARs		
Dose Interruptions			ARs in ≥5% (leading to dose interruptions)		
	BRAFTOVI	59%	• Diarrhea (17%) • Nausea (13%) • Musculoskeletal pain (8%) • Fatigue (8%)	• AST increased (7%) • ALT increased (6%) • Anemia (6%) • Hemorrhage (6%)	• Vomiting (6%) • Acute kidney injury (5%)
	MEKTOVI	62%	• Diarrhea (17%) • Nausea (15%) • Fatigue (9%) • AST increased (7%)	• ALT increased (6%) • Musculoskeletal pain (6%) • Vomiting (6%) • Anemia (6%)	• Acute kidney injury (5%) • Hemorrhage (5%) • Left ventricular dysfunction/ cardiomyopathy (5%)
Dose Reductions			ARs in ≥5% (leading to dose reductions)		
	BRAFTOVI	30%	• Diarrhea (8%) • Nausea (8%)	• AST increased (5%) • Fatigue (5%)	
	MEKTOVI	33%	• Diarrhea (8%) • Nausea (6%)	• AST increased (5%)	
Permanent Discontinuation			ARs in ≥2% (leading to permanent discontinuation)		
	BRAFTOVI	16%	• Diarrhea (3.1%) • Musculoskeletal pain (3.1%) • Fatigue (2%)	• Vomiting (2%) • Nausea (2%) • Rash (2%)	• Visual impairment (2%)
	MEKTOVI	17%	• Diarrhea (3.1%) • Musculoskeletal pain (2%) • Left ventricular dysfunction/ cardiomyopathy (2%)	• Fatigue (2%) • Nausea (2%) • Rash (2%) • Visual impairment (2%)	• Vomiting (2%)

- None of the other ARs leading to permanent discontinuation of BRAFTOVI or MEKTOVI occurred in more than 1 patient

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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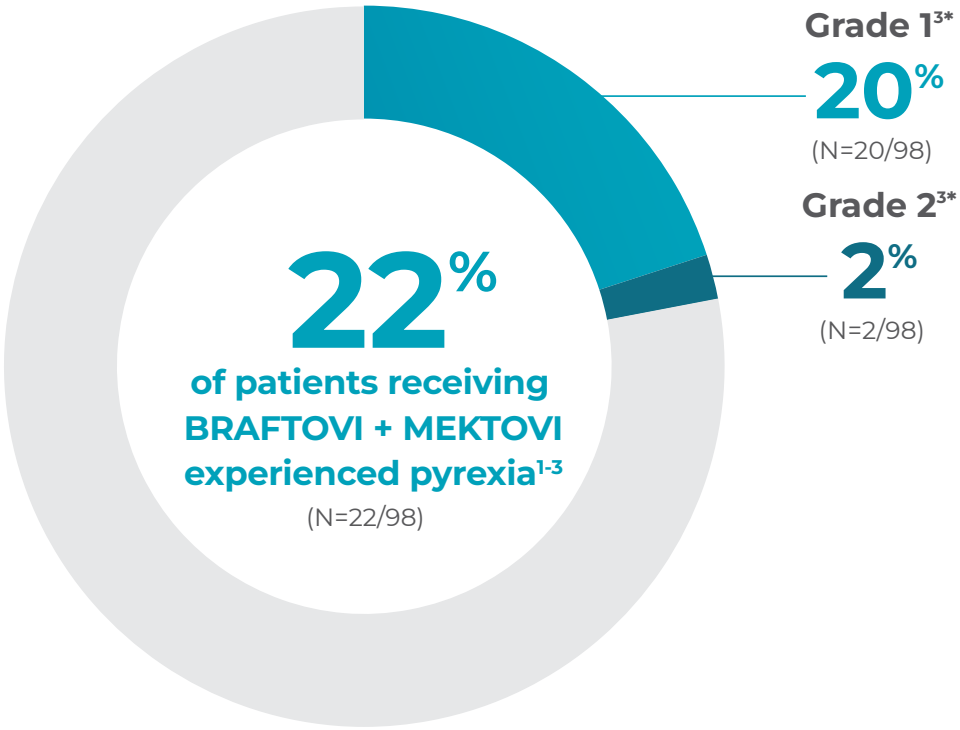
Incidence of pyrexia in patients receiving BRAFTOVI + MEKTOVI[1-3]



- All events of pyrexia were Grade 1 or 2 in severity, and none led to treatment discontinuation[1,2,4]

Fever[5,6]:

Grade 1: 100.4°F - 102.2°F (38.0°C - 39.0°C)
Grade 2: 102.3°F - 104.0°F (>39.0°C - 40.0°C)
Grade 3: >104.0°F (>40.0°C) for ≤24 hours
Grade 4: >104.0°F (>40.0°C) for >24 hours

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

Laboratory abnormalities[1,2]

Laboratory abnormalities occurred in ≥10% (all grades) of patients receiving BRAFTOVI + MEKTOVI*

	BRAFTOVI + MEKTOVI (N=98)	
Laboratory abnormality†	**All Grades**	**Grades 3/4**
Increased creatinine	91%	3.2%
Hyperglycemia	48%	6%
Anemia	47%	11%
Increased creatine kinase	41%	3.3%
Lipase increased	40%	14%
Increased ALT	34%	9%
Hypoalbuminemia	32%	0%
Increased alkaline phosphatase	31%	3.2%
Increased AST	31%	10%
Hyperkalemia	31%	2.1%
Hyponatremia	26%	11%
Lymphopenia	24%	6%
Serum amylase increased	22%	1.1%
Thrombocytopenia	20%	1.1%
Hypocalcemia	12%	2.1%
Leukopenia	12%	0%
Neutropenia	12%	1.1%

*Grades per National Cancer Institute CTCAE v4.03.

†Based on the number of patients with available baseline and at least one on-treatment laboratory test.

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

Monitoring patients for adverse reactions before and during treatment

Monitoring at treatment initiation and during treatment may help with adverse reaction management[1,2]

Before Treatment

Liver laboratory tests

Electrolytes: Correct hypokalemia and hypomagnesemia

CPK and creatinine levels

Echocardiogram/ MUGA scan: Assess ejection fraction

Ophthalmologic evaluation: Baseline assessment

Dermatologic evaluation

Regularly

Liver laboratory tests: Monthly during treatment

Electrolytes: Correct hypokalemia and hypomagnesemia

CPK and creatinine levels

Echocardiogram/MUGA scan: One month after initiating treatment, and every 2-3 months thereafter, assess ejection fraction

Ophthalmologic evaluation: Assess for visual symptoms at each visit. Perform ophthalmologic evaluation at regular intervals and for any visual disturbances, and to follow new or persistent ophthalmologic findings

Dermatologic evaluation: Every 2 months during treatment and for up to 6 months following discontinuation of treatment. Manage suspicious skin lesions with excisions and dermatopathologic evaluation

As clinically indicated

Liver laboratory tests

CPK and creatinine levels

Ophthalmologic evaluation: For new or worsening visual disturbances and to follow new or persistent ophthalmologic findings (for patient-reported acute vision loss or other visual disturbances within 24 hours)

Pulmonary evaluation: For new or progressive unexplained pulmonary symptoms or findings for possible interstitial lung disease

Additional monitoring considerations include[1,2]:

- **Monitor patients for new malignancies (including non-cutaneous) prior to initiation of treatment, while on treatment, and after discontinuation of treatment**
- **Monitor patients with cardiovascular risk factors**
- **Monitor patients who already have or who are at significant risk of developing QTc prolongation**
- **Monitor for drug-drug interactions**

CPK, creatine phosphokinase; MUGA, multi-gated acquisition.

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BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

Recommended dose reductions for adverse reactions

BRAFTOVI once daily[1,2]

Starting dose
450 mg
(6 capsules)

First reduction
300 mg
(4 capsules)

Second reduction
225 mg
(3 capsules)

If unable to tolerate 225 mg once daily, permanently discontinue BRAFTOVI

- If BRAFTOVI is permanently discontinued, discontinue MEKTOVI[2]

MEKTOVI twice daily[1,2]

Starting dose
45 mg
(3 tablets)

First reduction
30 mg
(2 tablets)

If unable to tolerate 30 mg twice daily, permanently discontinue MEKTOVI

- If MEKTOVI is withheld, reduce BRAFTOVI to a maximum dose of 300 mg once daily until MEKTOVI is resumed[1]

- Please refer to the **BRAFTOVI** and **MEKTOVI** US Prescribing Information for dosage modification and management specific to ARs

No need for a new prescription at dose adjustment[1,2]

START MONITOR MODIFY

Recommended dosage modifications for adverse reactions[1,2]

	Adverse reaction	Severity of adverse reaction*	Dose modification for BRAFTOVI® (encorafenib)	Dose modification for MEKTOVI® (binimetinib)
New primary malignancies	Non-cutaneous *RAS* mutation–positive malignancies	Any grade	**PERMANENTLY DISCONTINUE BRAFTOVI + MEKTOVI.**	
Ocular events	Serous retinopathy	Symptomatic serous retinopathy/retinal pigment epithelial detachment (RPED)	If MEKTOVI is withheld, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily until MEKTOVI is resumed. If MEKTOVI is permanently discontinued, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily.	**WITHHOLD MEKTOVI** for up to 10 days. If symptoms improve or patient becomes asymptomatic, resume at same dose. If symptoms do not improve, resume at a lower dose level or permanently discontinue MEKTOVI.
	Uveitis, including iritis and iridocyclitis	Grade 1: Asymptomatic; clinical or diagnostic observations only[6] Grade 2: Anterior uveitis; medical intervention indicated[6] Grade 3: Posterior or pan-uveitis[6]	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold BRAFTOVI + MEKTOVI for up to 6 weeks. If symptoms improve, resume at same or reduced dose. If symptoms do not improve, permanently discontinue BRAFTOVI + MEKTOVI.	
		Grade 4: Blindness (20/200 or worse) in the affected eye[6]	**PERMANENTLY DISCONTINUE BRAFTOVI + MEKTOVI.**	
	Retinal vein occlusion (RVO)	Any grade	If MEKTOVI is permanently discontinued, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily.	**PERMANENTLY DISCONTINUE MEKTOVI.**
Skeletal muscle effects	Rhabdomyolysis or CPK elevations	Grade 4 (>10 x ULN) asymptomatic CPK elevation[6] OR Any grade CPK elevation with symptoms or with renal impairment	If MEKTOVI is withheld, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily until MEKTOVI is resumed. If MEKTOVI is permanently discontinued, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily.	**WITHHOLD MEKTOVI** for up to 4 weeks. If symptoms improve to Grade 0-1, resume at a reduced dose. If not resolved within 4 weeks, permanently discontinue MEKTOVI.
Dermatologic	Dermatologic reactions (other than hand-foot skin reaction)	Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[6]	If no improvement within 2 weeks, **WITHHOLD BRAFTOVI + MEKTOVI** until Grade 0-1. Resume at same dose.	
		Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL[6]	**WITHHOLD BRAFTOVI + MEKTOVI** until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.	
		Grade 4: Life-threatening consequences; urgent intervention indicated[6]	**PERMANENTLY DISCONTINUE BRAFTOVI + MEKTOVI.**	

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

ADL, activities of daily living; ULN, upper limit of normal.

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

Recommended dosage modifications for adverse reactions[1,2]

START MONITOR MODIFY

	Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI® (encorafenib)	Dose modification for MEKTOVI® (binimetinib)
 Cardio-myopathy	Decreased left ventricular ejection fraction (LVEF)	Asymptomatic, absolute decrease in LVEF of >10% from baseline that is also below LLN	If MEKTOVI is withheld, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily until MEKTOVI is resumed. If MEKTOVI is permanently discontinued, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily.	**WITHHOLD MEKTOVI** for up to 4 weeks, evaluate LVEF every 2 weeks. Resume at a reduced dose if the following are present: · LVEF is at or above LLN and · Absolute decrease from baseline is 10% or less and · Patient is asymptomatic If the LVEF does not recover within 4 weeks, permanently discontinue MEKTOVI.
		Symptomatic congestive heart failure or absolute decrease in LVEF of >20% from baseline that is also below LLN	**REDUCE BRAFTOVI** by one dose level. If LVEF improves to at least institutional LLN and absolute decreases ≤10% compared to baseline, continue BRAFTOVI at the reduced dose. If no improvement, **WITHHOLD BRAFTOVI** until LVEF improves to at least institutional LLN and absolute decreases ≤10% compared to baseline; then resume at the reduced dose or reduce dose an additional dose level.	**PERMANENTLY DISCONTINUE MEKTOVI.**
 Cardiovascular	QTc prolongation	QTcF >500 ms and ≤60 ms increase from baseline	**WITHHOLD BRAFTOVI** until QTcF ≤500 ms. Resume at reduced dose. · If more than 1 recurrence, permanently discontinue BRAFTOVI	Dose modification of MEKTOVI when administered with BRAFTOVI is not recommended for QTc prolongation.
		QTcF >500 ms and >60 ms increase from baseline	**PERMANENTLY DISCONTINUE BRAFTOVI.**	
	Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE)	Grade 1: Venous thrombosis (eg, superficial thrombosis)[6] Grade 2: Venous thrombosis (eg, uncomplicated deep vein thrombosis); medical intervention indicated[6] Grade 3: Thrombosis (eg, uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus); medical intervention indicated[6] Grade 4: Life threatening (eg, pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated[6]	If MEKTOVI is withheld, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily until MEKTOVI is resumed. If MEKTOVI is permanently discontinued, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily.	**WITHHOLD MEKTOVI.** If symptoms improve to Grade 0-1, resume at a reduced dose. If no improvement, permanently discontinue MEKTOVI.
	Life-threatening PE			**PERMANENTLY DISCONTINUE MEKTOVI.**
 Hepatotoxicity	AST or ALT increased	Grade 2: >3.0 - 5.0 x ULN[6]	**MAINTAIN BRAFTOVI + MEKTOVI** dose. If no improvement within 4 weeks, **WITHHOLD BRAFTOVI + MEKTOVI** until improved to Grade 0-1 or to pretreatment/baseline levels; then resume at the same dose.	
		Grade 3: >5.0 - 20.0 x ULN[6] Grade 4: >20.0 x ULN[6]	Refer to Grade 3 or 4 guidance under *Other adverse reactions* on the following page.	

LLN, lower limit of normal; QTc, QT interval corrected; QTcF, QT interval corrected by Fridericia's formula.

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BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

Recommended dosage modifications for adverse reactions[1,2]

	Adverse reaction	Severity of adverse reaction	Dose modification for BRAFTOVI® (encorafenib)	Dose modification for MEKTOVI® (binimetinib)
 Respiratory	Interstitial lung disease	Grade 2	If MEKTOVI is withheld, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily until MEKTOVI is resumed. If MEKTOVI is permanently discontinued, **REDUCE BRAFTOVI** to a maximum dose of 300 mg once daily.	**WITHHOLD MEKTOVI** for up to 4 weeks. · If symptoms improve to Grade 0-1, resume at a reduced dose · If not resolved within 4 weeks, permanently discontinue MEKTOVI
		Grade 3 or Grade 4		**PERMANENTLY DISCONTINUE MEKTOVI.**
Other adverse reactions	Other ARs, including hemorrhage and hand-foot skin reaction*	Recurrent Grade 2 Or First occurrence of any Grade 3	**WITHHOLD BRAFTOVI + MEKTOVI** for up to 4 weeks. If symptoms improve to Grade 0-1 or to pretreatment/baseline level, resume at reduced dose. If no improvement, permanently discontinue BRAFTOVI + MEKTOVI.	
		First occurrence of any Grade 4	Permanently discontinue BRAFTOVI + MEKTOVI or **WITHHOLD BRAFTOVI + MEKTOVI** for up to 4 weeks. If symptoms improve to Grade 0-1 or to pretreatment/baseline level, then resume at reduced dose. If no improvement, permanently discontinue BRAFTOVI + MEKTOVI.	
		Recurrent Grade 3	**CONSIDER PERMANENTLY DISCONTINUING BRAFTOVI + MEKTOVI.**	
		Recurrent Grade 4	**PERMANENTLY DISCONTINUE BRAFTOVI + MEKTOVI.**	

***Dose modification of BRAFTOVI when administered with MEKTOVI is not recommended for the following ARs: new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; CPK elevation; rhabdomyolysis; and venous thromboembolism.**

Dose modification of MEKTOVI when administered with BRAFTOVI is not recommended for the following ARs: palmar-plantar erythrodysesthesia syndrome (PPES), non-cutaneous RAS mutation–positive malignancies, and QTc prolongation.

1. BRAFTOVI® (encorafenib) Prescribing Information. Array BioPharma, Inc.; December 2024. **2.** MEKTOVI® (binimetinib) Prescribing Information. Array BioPharma, Inc.; September 2024. **3.** Data on file. Pfizer Inc. **4.** Riely GJ, Smit EF, Ahn M-J, et al. Phase II, open-label study of encorafenib plus binimetinib in patients with *BRAF*^{V600}-mutant metastatic non-small-cell lung cancer. *J Clin Oncol*. 2023;41(21):3700-3711. **5.** Mandala M, Dummer R, Ascierto PA, et al. Characteristics of pyrexia with encorafenib (ENCO) plus binimetinib (BINI) in patients with BRAF-mutant melanoma. Poster presented at: The 15th International Congress of the Society for Melanoma Research; October 24-27, 2018; Manchester, UK. **6.** National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.03. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed July 30, 2024.

Please see additional IMPORTANT SAFETY INFORMATION on pages 2-3. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

YOUR TOOL TO HELP YOUR PATIENTS ON THEIR TREATMENT JOURNEY

START | **MONITOR** | **MODIFY**

A BRAF + MEK inhibitor combination with continuous dosing and no fasting or refrigeration requirements[1,2]

- BRAFTOVI and MEKTOVI must be stored at room temperature
- New prescription not needed for dose adjustments
- Avoid coadministration of strong or moderate CYP3A4 inhibitors (eg, grapefruit juice), strong CYP3A4 inducers, and CYP3A4 substrates with BRAFTOVI. Avoid coadministration of BRAFTOVI with drugs known to prolong the QT/QTc interval. Dose reductions of drugs that are substrates of OATP1B1, OATP1B3, or BCRP may be required when used concomitantly with BRAFTOVI

Select safety profile from the PHAROS trial[1,2]

- The most common ARs (≥25%) were fatigue (61%), nausea (58%), diarrhea (52%), musculoskeletal pain (48%), vomiting (37%), abdominal pain (32%), visual impairment (29%), constipation (27%), dyspnea (27%), rash (27%), and cough (26%)
- Serious ARs occurred in 38% of patients who received BRAFTOVI + MEKTOVI. Serious ARs occurring in ≥2% of patients were hemorrhage (6%), diarrhea (4.1%), anemia (3.1%), dyspnea (3.1%), pneumonia (3.1%), arrhythmia (2%), device related infection (2%), edema (2%), myocardial infarction (2%), and pleural effusion (2%)
- Fatal ARs occurred in 2% of patients who received BRAFTOVI + MEKTOVI, including intracranial hemorrhage (1%) and myocardial infarction (1%)

22% (n=22/98) of patients receiving BRAFTOVI + MEKTOVI experienced pyrexia in PHAROS[1-4]

- 20% experienced Grade 1 pyrexia; 2% experienced Grade 2
- All events of pyrexia were Grade 1 or 2 in severity, and none led to treatment discontinuation

SELECT IMPORTANT SAFETY INFORMATION

The Use of BRAFTOVI (encorafenib) + MEKTOVI (binimetinib) is associated with the following WARNINGS and PRECAUTIONS: New Primary Malignancies, Tumor Promotion in BRAF Wild-Type Tumors, Cardiomyopathy, Hepatotoxicity, Rhabdomyolysis, Hemorrhage, Venous Thromboembolism, Ocular Toxicities, QT Prolongation, Interstitial Lung Disease, Embryo-Fetal Toxicity, Risks Associated with BRAFTOVI as a Single Agent, and Risks Associated with Combination Treatment.

Learn more about BRAFTOVI + MEKTOVI at BraftoviHCP.com

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Pfizer Oncology

PP-BMK-USA-1084 February 2025