THERAPY MANAGEMENT GUIDE

To help support your patients with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation

INDICATIONS AND USAGE

BRAFTOVI® (encorafenib) and MEKTOVI® (binimetinib) are kinase inhibitors indicated for use in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.

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

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, cutaneous and non-cutaneous malignancies can occur. In the COLUMBUS trial, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6% and basal cell carcinoma occurred in 1.6% of patients. Median time to first occurrence of cuSCC/KA was 5.8 months. 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.

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.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

Dosage and administration[1,2]

Recommended starting dose[1,2]

Confirm the presence of unresectable or metastatic melanoma with a *BRAF* V600E/K mutation by an FDA-approved test before treatment.[1,2]

1st DOSE

BRAFTOVI® (encorafenib) 450 mg + **MEKTOVI® (binimetinib)** 45 mg

Six 75-mg BRAFTOVI capsules and three 15-mg MEKTOVI tablets

Product not to scale.

~12 HOURS APART

2nd DOSE

MEKTOVI 45 mg

Three 15-mg MEKTOVI tablets

Product not to scale.

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

- BRAFTOVI may be taken in the morning or the 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]

Missed dose[1,2]

Instruct patients not to take a missed dose of:

BRAFTOVI within 12 hours of the next dose **12 hours**

MEKTOVI within 6 hours of the next dose **6 hours**

- In case of vomiting, do not take an additional dose of BRAFTOVI + MEKTOVI; resume dosing with the next scheduled dose[1,2]

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. In the COLUMBUS trial, evidence of cardiomyopathy occurred in 7% and Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) was 3.6 months. Cardiomyopathy resolved in 87% 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.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Dosage and administration[1,2] (cont)

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

May be taken with or without food*

No refrigeration requirement†

Continuous dosing schedule

*Avoid coadministration of strong or moderate CYP3A4 inhibitors (eg, grapefruit juice) and inducers with BRAFTOVI.[1]
†BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib) must be stored at room temperature.[1,2]

Selected BRAFTOVI drug interactions[1]

Strong or moderate CYP3A4 inhibitors	Coadministration increases BRAFTOVI plasma concentrations and may increase BRAFTOVI adverse reactions. Avoid coadministration; however, if unavoidable, reduce BRAFTOVI dose.
Strong or moderate CYP3A4 inducers	Coadministration may decrease BRAFTOVI plasma concentration and may decrease BRAFTOVI efficacy. Avoid coadministration.
Sensitive CYP3A4 substrates	Coadministration with BRAFTOVI may increase adverse reactions or decrease efficacy of these agents.
	Coadministration with hormonal contraceptives can result in decreased concentrations and loss of hormonal contraceptive efficacy. Avoid coadministration.

CYP3A4, cytochrome P450 3A4.

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

Recommended dose reductions for BRAFTOVI for coadministration with strong or moderate CYP3A4 inhibitors[1]

Current daily dose‡	Dose for coadministration with moderate CYP3A4 inhibitor	Dose for coadministration with strong CYP3A4 inhibitor
450 mg	225 mg	150 mg
300 mg	150 mg	75 mg
225 mg	75 mg	75 mg

‡Current daily dose refers to recommended dose of BRAFTOVI based on indication or reductions for adverse reactions (ARs) based on dosing recommendations in the table on page 9.[1]

See recommended dose adjustments for adverse reactions starting on page 9.

IMPORTANT SAFETY INFORMATION (CONT)
WARNINGS AND PRECAUTIONS (CONT)
Venous Thromboembolism (VTE): In the COLUMBUS trial, VTE occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Adverse reactions observed in the COLUMBUS trial[1,2]

See trial design on page 5.

- The most common adverse reactions (≥25%) observed with BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib) were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), and arthralgia (26%)

Adverse reactions occurring in ≥10% of patients (all grades)[1,2]*

Trial Arm	BRAFTOVI + MEKTOVI (n=192)		vemurafenib (n=186)	
Severity of Adverse Reaction	**All Grades**	**Grades 3/4†**	**All Grades**	**Grades 3/4†**
General Disorders and Administration Site Conditions				
Fatigue‡	**43%**	**3%**	46%	6%
Pyrexia‡	**18%**	**4%**	30%	0%
Peripheral edema‡	**13%**	**1%**	15%	1%
Gastrointestinal Disorders				
Nausea	**41%**	**2%**	34%	2%
Diarrhea	**36%**	**3%**	34%	2%
Vomiting‡	**30%**	**2%**	16%	1%
Abdominal pain‡	**28%**	**4%**	16%	1%
Constipation	**22%**	**0%**	6%	1%
Musculoskeletal and Connective Tissue Disorders				
Arthralgia‡	**26%**	**1%**	46%	6%
Myopathy‡	**23%**	**0%**	22%	1%
Pain in extremity	**11%**	**1%**	13%	1%
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis‡	**23%**	**1%**	49%	1%
Rash‡	**22%**	**1%**	53%	13%
Dry skin‡	**16%**	**0%**	26%	0%
Alopecia‡	**14%**	**0%**	38%	0%
Pruritus‡	**13%**	**1%**	21%	1%
Nervous System Disorders				
Headache‡	**22%**	**2%**	20%	1%
Dizziness‡	**15%**	**3%**	4%	0%
Peripheral neuropathy‡	**12%**	**1%**	13%	2%
Visual Disorders				
Visual impairment‡	**20%**	**0%**	4%	0%
Serous retinopathy/RPED‡	**20%**	**3%**	2%	0%
Vascular Disorders				
Hemorrhage‡	**19%**	**3%**	9%	2%
Hypertension‡	**11%**	**6%**	11%	3%

*Grades per NCI CTCAE v4.03.
†Grade 4 adverse reactions limited to hemorrhage (n=3), diarrhea (n=1), fatigue (n=1), pruritus (n=1), and rash (n=1) in the BRAFTOVI + MEKTOVI arm and constipation (n=1) in the vemurafenib arm.
‡Represents a composite of multiple, related preferred terms.
NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RPED, retinal pigment epithelial detachment.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Adverse reactions observed in the COLUMBUS trial[1,2] (cont)

Treatment-emergent lab abnormalities occurring in ≥10% of patients (all grades)[1,2*]

Trial Arm	BRAFTOVI + MEKTOVI (n=192)		vemurafenib (n=186)	
Severity of Lab Abnormality	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
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 creatine phosphokinase	**58%**	**5%**	3.8%	0%
Increased gamma glutamyl transferase	**45%**	**11%**	34%	4.8%
Increased ALT	**29%**	**6%**	27%	2.2%
Hyperglycemia	**28%**	**5%**	20%	2.7%
Increased AST	**27%**	**2.6%**	24%	1.6%
Increased alkaline phosphatase	**21%**	**0.5%**	35%	2.2%
Hyponatremia	**18%**	**3.6%**	15%	0.5%
Hypermagnesemia	**10%**	**1%**	26%	0.5%

*Grades per NCI CTCAE v4.03.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

5% of patients who received BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib) permanently discontinued treatment due to adverse reactions[1,2]

- The most common adverse reactions resulting in permanent discontinuation were hemorrhage (2%) and headache (1%)

Trial design[1-3]

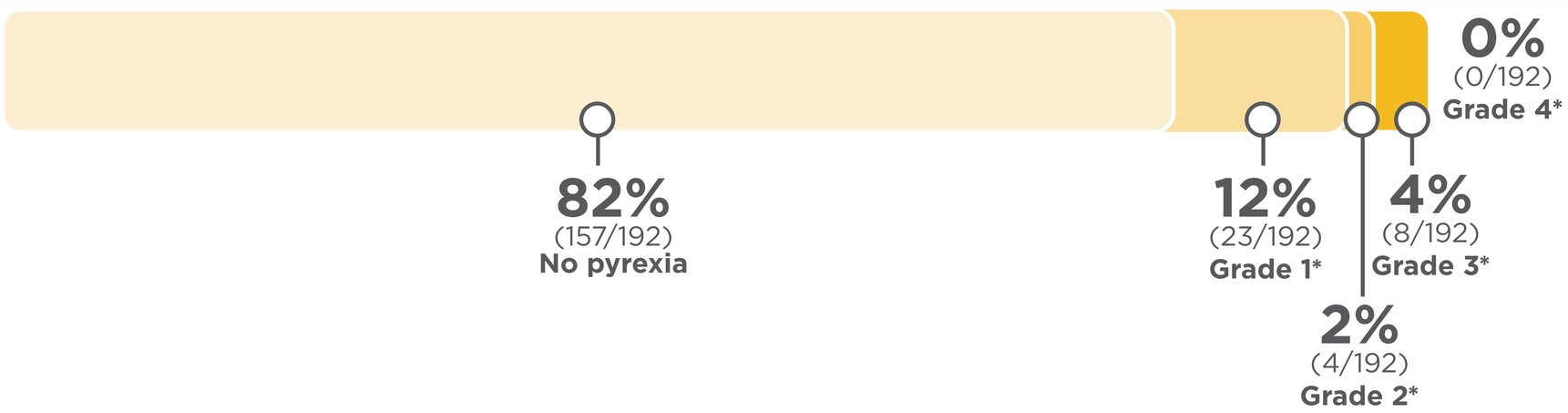
COLUMBUS was a Phase 3, global, randomized (1:1:1), active-controlled, open-label, multicenter clinical trial of 577 adults with *BRAF* V600E/K–mutation-positive unresectable or metastatic melanoma. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Patients received BRAFTOVI 450 mg once daily + MEKTOVI 45 mg twice daily (n=192), BRAFTOVI (n=194), or vemurafenib 960 mg twice daily (n=191). The major efficacy outcome measure was progression-free survival (PFS) as assessed by a blinded independent central review (BICR). Overall survival (OS), objective response rate (ORR), and duration of response (DoR) were additional efficacy outcome measures (ORR and DoR per BICR). Treatment was continued until disease progression or unacceptable toxicity. Only combination dosing of BRAFTOVI + MEKTOVI is approved for use in *BRAF* V600E/K–mutation-positive unresectable or metastatic melanoma. Please visit braftovimektovi.com/hcp for additional details.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Pyrexia observed with BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

- The rates of pyrexia in patients who received BRAFTOVI + MEKTOVI vs vemurafenib were **18% vs 30% (all grades)** and **4% vs 0% (Grades 3/4)**[1,2]
- Dose interruptions of BRAFTOVI due to pyrexia occurred in **4% of patients**[1,4]
- Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with MEKTOVI[1]
  — The most common were nausea (7%), vomiting (7%), and pyrexia (4%)
- Less than 1% of patients who received BRAFTOVI + MEKTOVI (1/192) discontinued treatment due to pyrexia[5]

Incidence of pyrexia in the COLUMBUS trial with BRAFTOVI + MEKTOVI[5]



Fever: 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.[6]

*Per NCI CTCAE v4.03.

For more information on dose reductions or interruptions from the COLUMBUS trial, see page 9.

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Hemorrhage: Hemorrhage can occur when BRAFTOVI is administered in combination with MEKTOVI. In the COLUMBUS trial, hemorrhage occurred in 19% of patients and ≥ Grade 3 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Ocular adverse reactions observed with BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

- Ocular adverse reactions were proactively monitored in the COLUMBUS trial[4]

Serous retinopathy/retinal pigment epithelial detachment (RPED)	Uveitis	Retinal vein occlusion (RVO)*
Incidence		
• Occurred in **20%** of patients[2] – 8% were retinal detachment and 6% were macular edema[2] – Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness[2] – Majority of cases were asymptomatic and were detected due to proactive monitoring during the trial[2,4] • Median time to onset was **1.2 months**—however, it could occur as soon as the first day of dosing (range 0 to 17.5 months)[2]	• Occurred in **4%** of patients[1,2] • Median time to onset was **4.4 months** (range 0.5 to 11.2 months)[4]	• Occurred in **0.1%** of patients (1 of 690 patients)[2]
Some common symptoms[7–9]		
• Distorted, dimmed, or blurred central vision • A dark area within one's central vision • Straight lines appear bent, crooked, or irregular • Objects appear smaller or farther away than they are • White objects appear to have a brownish tinge or appear duller in color	• Eye redness • Eye pain • Light sensitivity • Blurred vision • Floaters • Decreased vision	• Usually sudden—but sometimes gradual—painless vision loss

These are not all the possible symptoms of these conditions.

***The safety of MEKTOVI has not been established in patients with a history of RVO or current risk factors for RVO.**

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Ocular Toxicities: In the COLUMBUS trial, serous retinopathy occurred in 20% of patients; 8% were retinal detachment and 6% were macular edema. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. 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 encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI (n=690), 1 patient experienced RVO (0.1%). 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. In COLUMBUS, uveitis, including iritis and iridocyclitis was reported in 4% of patients treated with MEKTOVI in combination with BRAFTOVI. 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 IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Monitoring patients for adverse reactions during treatment[1,2]

Monitoring at treatment initiation and during treatment may help with adverse reaction management.

Before treatment

LFT

Electrolytes: Correct hypokalemia and hypomagnesemia

Creatinine with CPK

Echocardiogram/MUGA scan

Ophthalmologic evaluation: Baseline assessment

Dermatologic evaluation

Regularly

LFT: Every month

Electrolytes: Correct hypokalemia and hypomagnesemia

Creatinine with CPK

Echocardiogram/MUGA scan: 1 month after treatment initiation and every 2-3 months thereafter

Visual symptom assessment: Every visit

Ophthalmologic evaluation

Dermatologic evaluation: Every 2 months during treatment and for up to 6 months following discontinuation of treatment

As clinically indicated

LFT

Creatinine with CPK

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

Pulmonary evaluation: For new or progressive unexplained pulmonary symptoms or findings

CPK, creatine phosphokinase; LFT, liver function test; MUGA, multigated acquisition.

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Interstitial Lung Disease (ILD): ILD, including pneumonitis occurred in 0.3% (2 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. 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 COLUMBUS trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. No patient experienced Grade 3 or 4 serum bilirubin elevation. Monitor liver laboratory tests before initiation of MEKTOVI, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Recommended dose adjustments for adverse reactions[1,2]

No need for a new prescription at dose adjustment

BRAFTOVI® (encorafenib) once daily

Starting dose	First reduction	Second reduction	
450 mg (6 capsules)	**300 mg** (4 capsules)	**225 mg** (3 capsules)	**If unable to tolerate 225 mg QD, permanently discontinue BRAFTOVI** • If BRAFTOVI is permanently discontinued, discontinue MEKTOVI[2]

MEKTOVI® (binimetinib) twice daily

Starting dose	First reduction	
45 mg (3 tablets)	**30 mg** (2 tablets)	**If unable to tolerate 30 mg BID, permanently discontinue MEKTOVI** • If MEKTOVI is withheld, reduce BRAFTOVI to a maximum dose of 300 mg once daily until MEKTOVI is resumed[1]

For more information on dosage modifications for BRAFTOVI and MEKTOVI, see pages 10-12.

Median time to first dose reduction/interruption with BRAFTOVI + MEKTOVI was 6.9 months (95% CI: 3.1-10.7) vs 1.8 months (95% CI: 1.0-3.3) with vemurafenib[4]

- In the COLUMBUS trial, this analysis was not pre-specified and is descriptive in nature only
- Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with MEKTOVI[1]
  — 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 MEKTOVI[1]
  — The most common were arthralgia (2%), fatigue (2%), and nausea (2%)
- Adverse reactions leading to dose interruptions of MEKTOVI occurred in 33% of patients receiving MEKTOVI in combination with BRAFTOVI[2]
  — The most common were left ventricular dysfunction (6%) and serous retinopathy (5%)
- Adverse reactions leading to dose reductions of MEKTOVI occurred in 19% of patients receiving MEKTOVI in combination with BRAFTOVI[2]
  — The most common were left ventricular dysfunction (3%), serous retinopathy (3%), and colitis (2%)

BID, twice daily; CI, confidence interval; QD, once daily.

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Rhabdomyolysis: Rhabdomyolysis can occur when MEKTOVI is administered in combination with BRAFTOVI. In the COLUMBUS trial, elevation of laboratory values of serum CPK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% (1 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. 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.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Recommended dosage modifications for adverse reactions[1,2]

	Adverse reaction	Severity of adverse reaction (NCI CTCAE v4.03)	Dose modification for BRAFTOVI® (encorafenib)	Dose modification for MEKTOVI® (binimetinib)
New primary malignancies	**Non-cutaneous *RAS* mutation positive malignancies**	Any grade	**Permanently discontinue BRAFTOVI and 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 improves and becomes asymptomatic, resume at same dose • If not improved, resume at a lower dose level or permanently discontinue
	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]	**Withhold BRAFTOVI and MEKTOVI** for up to 6 weeks if Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis. • If improved, resume at same or reduced dose • If not improved, permanently discontinue BRAFTOVI and MEKTOVI	
		Grade 4: Blindness (20/200 or worse) in the affected eye[6]	**Permanently discontinue BRAFTOVI and 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)[6] asymptomatic CPK elevation 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 improved 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]	**Maintain BRAFTOVI** If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose.	**Maintain MEKTOVI** If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
		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 and 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 and MEKTOVI.**	

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

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

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Recommended dosage modifications for adverse reactions[1,2] (cont)

	Adverse reaction	Severity of adverse reaction (NCI CTCAE v4.03)	Dose modification for BRAFTOVI® (encorafenib)	Dose modification for MEKTOVI® (binimetinib)
Cardiomyopathy	**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 the LLN and • Absolute decrease from baseline is 10% or less and • Patient is asymptomatic If 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	If MEKTOVI is permanently discontinued, **reduce BRAFTOVI** to a maximum dose of 300 mg once daily.	**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 one recurrence, permanently discontinue	If BRAFTOVI is permanently discontinued, **discontinue MEKTOVI**.
		QTcF >500 ms and >60 ms increase from baseline	**Permanently discontinue BRAFTOVI and MEKTOVI.**	
	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 improves to Grade 0-1, resume at a reduced dose • If no improvement, permanently discontinue
	Life-threatening PE		If MEKTOVI is permanently discontinued, **reduce BRAFTOVI** to a maximum dose of 300 mg once daily.	**Permanently discontinue MEKTOVI.**
Hepatotoxicity	**AST or ALT increased**	Grade 2: >3.0 - 5.0 x ULN[6]	**Maintain BRAFTOVI** If no improvement within 4 weeks, withhold until improved to Grade 0-1 or to pretreatment/baseline levels, and then resume at the same dose. **Note:** If MEKTOVI is withheld, **reduce BRAFTOVI** to a maximum dose of 300 mg once daily until MEKTOVI is resumed.	**Maintain MEKTOVI** If no improvement within 2 weeks, withhold until improved to Grade 0-1 or to pretreatment/baseline levels, and 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 ARs* on page 12.	

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

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

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Recommended dosage modifications for adverse reactions[1,2] (cont)

	Adverse reaction	Severity of adverse reaction (NCI CTCAE v4.03)	Dose modification for BRAFTOVI® (encorafenib)	Dose modification for MEKTOVI® (binimetinib)
Respiratory	Interstitial lung disease	Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[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** for up to 4 weeks. • If improved to Grade 0-1, resume at a reduced dose • If not resolved within 4 weeks, permanently discontinue
		Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL[6] Grade 4: Life-threatening consequences; urgent intervention indicated[6]	If MEKTOVI is permanently discontinued, **reduce BRAFTOVI** to a maximum dose of 300 mg once daily.	**Permanently discontinue MEKTOVI.**
Other ARs, including hemorrhage and hand-foot skin reaction*		Recurrent Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[6] OR First occurrence of any Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[6]	**Withhold BRAFTOVI and MEKTOVI** for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at a reduced dose • If no improvement, permanently discontinue	
		First occurrence of any Grade 4: Life-threatening consequences; urgent intervention indicated[6]	**Permanently discontinue or withhold BRAFTOVI and MEKTOVI** for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at a reduced dose • If no improvement, permanently discontinue	
		Recurrent Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[6]	**Consider permanently discontinuing BRAFTOVI and MEKTOVI.**	
		Recurrent Grade 4: Life-threatening consequences; urgent intervention indicated[6]	**Permanently discontinue BRAFTOVI and MEKTOVI.**	

Maintain | Reduce or withhold | Permanently discontinue

***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; cardiac dysfunction; 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.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

BRAFTOVI + MEKTOVI is available through specific specialty pharmacies

To help your patients access the medication you've prescribed, we can provide a list of specialty pharmacies.

Visit PfizerOncologyTogether.com to see the complete list of specialty pharmacies in the BRAFTOVI + MEKTOVI distribution network.

Pfizer does not influence or advocate for the use of any one specialty pharmacy and makes no representation or guarantee of services or coverage of any product.

Product not to scale.

BRAFTOVI is supplied as 75-mg capsules[1]

- 75-mg capsules are available in:
  - Cartons containing 2 bottles of 90 capsules
  - Cartons containing 2 bottles of 60 capsules

Product not to scale.

MEKTOVI is supplied as 15-mg tablets[2]

- 15-mg tablets are available in cartons containing 1 bottle of 180 tablets

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

QTc Prolongation: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the COLUMBUS trial, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination 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.

Embryo-Fetal Toxicity: BRAFTOVI and MEKTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Nonhormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI + 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. Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% in patients treated with BRAFTOVI in combination with MEKTOVI. If MEKTOVI is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

A free 15-day trial of BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib) is available for new patients

To utilize this voucher, a patient must have a valid prescription. There is no obligation to continue BRAFTOVI + MEKTOVI. To continue a patient on therapy, a separate prescription must be written to be filled at the patient's participating pharmacy of choice. Patients may be offered enrollment in the trial voucher exclusively through their healthcare provider.

By redeeming this voucher, you acknowledge that the patient currently meets the eligibility criteria and will comply with the terms & conditions described below:

- The patient will receive a 15-day supply of BRAFTOVI and MEKTOVI.
- Only new patients may use this voucher. By redeeming this voucher, you certify the patient is not currently using BRAFTOVI and MEKTOVI.
- An original voucher and valid prescription must be presented to the pharmacy.
- **The voucher will be accepted only at participating pharmacies.**
- **The patient must not submit any claim for reimbursement for product dispensed pursuant to this voucher to any third-party payor, including Medicare, Medicaid, or any other federal or state health care program. The patient cannot apply the value of the free product received through this voucher toward any government insurance benefit out-of-pocket spending calculations, such as Medicare Part D True Out-of-Pocket Costs (TrOOP).**
- The patient must be 18 years of age or older to redeem the voucher.
- This voucher is not valid where prohibited by law.
- This voucher cannot be combined with any other savings, free trial or similar offer for the specified prescription. This voucher should not be combined with samples for the specified prescription.
- **This free trial voucher is not health insurance.** This free trial voucher is not intended to address delays or gaps in health insurance coverage for the specified prescription.
- Offer good only in the U.S. and Puerto Rico.
- No purchase is necessary.
- Patients have no obligation to continue to use BRAFTOVI and MEKTOVI.
- Array BioPharma reserves the right to rescind, revoke or amend this offer without notice.
- This voucher expires 12/31/2021.
- To Pharmacist: Redeem only when affixed to valid signed prescriptions for BRAFTOVI and MEKTOVI. Submit claim for maximum 15 days of BRAFTOVI and MEKTOVI for PDM. Your patient will receive 15 days of BRAFTOVI and MEKTOVI at no charge. For pharmacy processing questions, please call 1-877-488-0001.

IMPORTANT SAFETY INFORMATION (CONT)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%, all grades, in the COLUMBUS trial) for BRAFTOVI and MEKTOVI compared to vemurafenib were: fatigue (43% vs. 46%), nausea (41% vs. 34%), diarrhea (36% vs. 34%), vomiting (30% vs. 16%), abdominal pain (28% vs. 16%), arthralgia (26% vs. 46%), myopathy (23% vs. 22%), hyperkeratosis (23% vs. 49%), rash (22% vs. 53%), headache (22% vs. 20%), constipation (22% vs. 6%), visual impairment (20% vs. 4%), serous retinopathy/RPED (20% vs. 2%). Other clinically important adverse reactions occurring in <10% of patients in the COLUMBUS trial were facial paresis, pancreatitis, panniculitis, drug hypersensitivity, and colitis.

In the COLUMBUS trial, the most common laboratory abnormalities (all grades) (≥ 20%) for BRAFTOVI and MEKTOVI compared to vemurafenib included increased creatinine (93% vs. 92%), increased creatine phosphokinase (58% vs. 3.8%), increased gamma glutamyl transferase (GGT) (45% vs. 34%), anemia (36% vs. 34%), increased ALT (29% vs. 27%), hyperglycemia (28% vs. 20%), increased AST (27% vs. 24%), and increased alkaline phosphatase (21% vs. 35%).

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Pfizer Oncology together™

Making your patients' support needs a priority. Together.

At Pfizer Oncology Together, patient support is at the core of everything we do. We've gathered resources and developed tools to help patients and their loved ones throughout BRAFTOVI + MEKTOVI treatment.

Personalized patient support

When your patients need support for their day-to-day challenges, we want to be a place they can turn to for help. At Pfizer Oncology Together, our Care Champions, who have social work experience, can connect patients prescribed BRAFTOVI + MEKTOVI to resources that may help with some of their daily needs.*

- Connections to emotional support resources such as diagnosis-specific support groups, an independent organization's helpline, and a free app to connect with loved ones
- Connections to independent organizations that help eligible patients find free rides and lodging for treatment-related appointments
- Educational information about physical and mental health, nutrition, and BRAFTOVI + MEKTOVI
- Information to help patients prepare for leaving or returning to work

FOR LIVE, PERSONALIZED SUPPORT
Call **1-877-744-5675** (Monday–Friday 8 AM–8 PM ET)

VISIT
PfizerOncologyTogether.com

A free app designed to help manage life with cancer

Help your patients and their caregivers stay connected and get organized by telling them about **LivingWith**™, a free app developed by Pfizer Oncology, designed to help manage life with cancer.

Download **LivingWith** for free. Available in English and Spanish.

LIVINGWITH®

The **LivingWith**™ app is available to anyone living with cancer and their loved ones, and is not specific to BRAFTOVI + MEKTOVI.

*Some services are provided through third-party organizations that operate independently and are not controlled by Pfizer. Availability of services and eligibility requirements are determined solely by these organizations.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Pfizer Oncology together™

Patient financial assistance

Commercially insured

Resources for eligible patients with commercial, private, employer, or state health insurance marketplace coverage:

- Co-pay assistance: Eligible, commercially insured patients may pay as little as $0 per month for BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib). Limits, terms, and conditions apply.* There are no income requirements, forms, or faxing to enroll

*Patients are not eligible to use this card if they are enrolled in a state or federally funded insurance program, including but not limited to Medicare, Medicaid, TRICARE, Veterans Affairs health care, a state prescription drug assistance program, or the Government Health Insurance Plan available in Puerto Rico. Patients may receive up to $25,000 per product in savings annually. **The offer will be accepted only at participating pharmacies.** This offer is not health insurance. No membership fees apply. Pfizer reserves the right to rescind, revoke, or amend this offer without notice. For full Terms and Conditions, please see PfizerOncologyTogether.com/terms. For any questions, please call 1-877-744-5675, visit PfizerOncologyTogether.com/terms or write: Pfizer Oncology Together Co-Pay Savings Program, 2250 Perimeter Park Drive, Suite 300, Morrisville, NC 27560.

Medicare/Government insured

Help identifying resources for eligible patients with Medicare/Medicare Part D, Medicaid, and other government insurance plans:

- Assistance for patients with searching for financial support that may be available from independent charitable foundations. These foundations exist independently of Pfizer and have their own eligibility criteria and application processes. Availability of support from the foundations is determined solely by the foundations
- Financial help through Extra Help, a Medicare Part D Low-Income Subsidy (LIS) program
- Free medication†

Uninsured

Help identifying resources for eligible patients without any form of healthcare coverage:

- Help finding coverage
- Free medication through the Pfizer Patient Assistance Program, or at a savings through the Pfizer Savings Program‡

†If support from independent charitable foundations or Medicare Extra Help is not available, Pfizer Oncology Together will provide eligible patients with medication for free through the Pfizer Patient Assistance Program. The Pfizer Patient Assistance Program is a joint program of Pfizer Inc. and the Pfizer Patient Assistance Foundation™. The Pfizer Patient Assistance Foundation is a separate legal entity from Pfizer Inc. with distinct legal restrictions.

‡**The Pfizer Savings Program is not health insurance. For more information, call the toll-free number 1-877-744-5675.** There are no membership fees to participate in this program. Estimated savings are 50% and depend on such factors as the particular drug purchased, amount purchased, and the pharmacy where purchased.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

Supporting your patients starting on BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib)

To help your patients start on therapy, helpful resources can be found in the BRAFTOVI + MEKTOVI Patient Starter Kit

The Patient Starter Kit does not include BRAFTOVI + MEKTOVI.

This kit contains the following resources to help your patients during treatment with BRAFTOVI + MEKTOVI:

- Welcome Letter
- BRAFTOVI + MEKTOVI Patient Brochure
- Journal and Calendar
- Two Pill Trackers, one to be placed on the bottle of BRAFTOVI (green tracker) and one to be placed on the bottle of MEKTOVI (burgundy tracker)
- Zippered Bag, designed to keep all your patient's treatment-related materials in one place
- BRAFTOVI + MEKTOVI Drug Information Card

For more patient resources, as well as additional information on BRAFTOVI + MEKTOVI, please refer your patients to Tovi2.com

To obtain a starter kit for your patient, contact your local representative or contact us at **braftovimektovi.com/hcp**.

IMPORTANT SAFETY INFORMATION (CONT)

DRUG INTERACTIONS

Avoid concomitant use of strong or moderate CYP3A4 inhibitors or inducers and sensitive CYP3A4 substrates with BRAFTOVI. Modify BRAFTOVI dose if concomitant use of strong or moderate CYP3A4 inhibitors cannot be avoided. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20.

IMPORTANT SAFETY INFORMATION and INDICATION

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, cutaneous and non-cutaneous malignancies can occur. In the COLUMBUS trial, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6% and basal cell carcinoma occurred in 1.6% of patients. Median time to first occurrence of cuSCC/KA was 5.8 months. 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.

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, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. In the COLUMBUS trial, evidence of cardiomyopathy occurred in 7% and Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) was 3.6 months. Cardiomyopathy resolved in 87% 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.

Venous Thromboembolism (VTE): In the COLUMBUS trial, VTE occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism. 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 COLUMBUS trial, hemorrhage occurred in 19% of patients and ≥ Grade 3 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Ocular Toxicities: In the COLUMBUS trial, serous retinopathy occurred in 20% of patients; 8% were retinal detachment and 6% were macular edema. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. 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 encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI (n=690), 1 patient experienced RVO (0.1%). 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. In COLUMBUS, uveitis, including iritis and iridocyclitis was reported in 4% of patients treated with MEKTOVI in combination with BRAFTOVI. 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.

IMPORTANT SAFETY INFORMATION continues on next page.

IMPORTANT SAFETY INFORMATION and INDICATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Interstitial Lung Disease (ILD): ILD, including pneumonitis occurred in 0.3% (2 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. 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 COLUMBUS trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. No patient experienced Grade 3 or 4 serum bilirubin elevation. Monitor liver laboratory tests before initiation of 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 COLUMBUS trial, elevation of laboratory values of serum CPK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% (1 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. 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.

QTc Prolongation: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the COLUMBUS trial, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination 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.

Embryo-Fetal Toxicity: BRAFTOVI and MEKTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Nonhormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI + 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. Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% in patients treated with BRAFTOVI in combination with MEKTOVI. If MEKTOVI is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended.

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%, all grades, in the COLUMBUS trial) for BRAFTOVI and MEKTOVI compared to vemurafenib were: fatigue (43% vs. 46%), nausea (41% vs. 34%), diarrhea (36% vs. 34%), vomiting (30% vs. 16%), abdominal pain (28% vs. 16%), arthralgia (26% vs. 46%), myopathy (23% vs. 22%), hyperkeratosis (23% vs. 49%), rash (22% vs. 53%), headache (22% vs. 20%), constipation (22% vs. 6%), visual impairment (20% vs. 4%), serous retinopathy/RPED (20% vs. 2%). Other clinically important adverse reactions occurring in <10% of patients in the COLUMBUS trial were facial paresis, pancreatitis, panniculitis, drug hypersensitivity, and colitis.

In the COLUMBUS trial, the most common laboratory abnormalities (all grades) (≥ 20%) for BRAFTOVI and MEKTOVI compared to vemurafenib included increased creatinine (93% vs. 92%), increased creatine phosphokinase (58% vs. 3.8%), increased gamma glutamyl transferase (GGT) (45% vs. 34%), anemia (36% vs. 34%), increased ALT (29% vs. 27%), hyperglycemia (28% vs. 20%), increased AST (27% vs. 24%), and increased alkaline phosphatase (21% vs. 35%).

IMPORTANT SAFETY INFORMATION continues on next page.

IMPORTANT SAFETY INFORMATION and INDICATION (CONT)

DRUG INTERACTIONS

Avoid concomitant use of strong or moderate CYP3A4 inhibitors or inducers and sensitive CYP3A4 substrates with BRAFTOVI. Modify BRAFTOVI dose if concomitant use of strong or moderate CYP3A4 inhibitors cannot be avoided. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval.

INDICATIONS AND USAGE

BRAFTOVI® (encorafenib) and MEKTOVI® (binimetinib) are kinase inhibitors indicated for use in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.

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

Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

References: 1. BRAFTOVI® (encorafenib) Prescribing Information. Array BioPharma, Inc.; April 2020. **2.** MEKTOVI® (binimetinib) Prescribing Information. Array BioPharma, Inc.; October 2020. **3.** Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615. **4.** Data on file. Pfizer, Inc. **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. National Cancer Institute. National Institutes of Health. Accessed July 13, 2020. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf **7.** Mehta S. Central retinal vein occlusion and branch retinal vein occlusion. Merck Manual. Revised June 2020. Accessed July 16, 2020. https://www.merckmanuals.com/professional/eye-disorders/retinal-disorders/central-retinal-vein-occlusion-and-branch-retinal-vein-occlusion **8.** Uveitis. Mayo Clinic. Accessed February 20, 2020. https://www.mayoclinic.org/diseases-conditions/uveitis/symptoms-causes/syc-20378734 **9.** Porter D. What is central serous chorioretinopathy? American Academy of Ophthalmology. Published September 4, 2019. Accessed February 20, 2020. https://www.aao.org/eye-health/diseases/what-is-central-serous-retinopathy

SUPPORTING YOUR PATIENTS THROUGH THEIR TREATMENT WITH

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

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

*BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib) must be stored at room temperature.[1,2]
†Avoid coadministration of strong or moderate CYP3A4 inhibitors (eg, grapefruit juice) and inducers with BRAFTOVI.[1]

5% of patients who received BRAFTOVI + MEKTOVI permanently discontinued treatment due to adverse reactions[1,2]

- The most common adverse reactions resulting in permanent discontinuation were hemorrhage (2%) and headache (1%)
- The most common adverse reactions (≥25%) vs vemurafenib were fatigue (43% vs 46%), nausea (41% vs 34%), diarrhea (36% vs 34%), vomiting (30% vs 16%), abdominal pain (28% vs 16%), and arthralgia (26% vs 46%)

The rates of pyrexia in patients who received BRAFTOVI + MEKTOVI vs vemurafenib were 18% vs 30% (all grades) and 4% vs 0% (Grades 3/4)[1,2]

- Dose interruptions of BRAFTOVI due to pyrexia occurred in 4% of patients[1,4]
- Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with MEKTOVI[1]
  — The most common were nausea (7%), vomiting (7%), and pyrexia (4%)
- 6% of all patients who received BRAFTOVI + MEKTOVI (12/192) experienced pyrexia Grade 2 or higher[5]
- Less than 1% of patients who received BRAFTOVI + MEKTOVI (1/192) discontinued treatment due to pyrexia[5]

For more information on dose reductions or interruptions from the COLUMBUS trial, see page 9.

IMPORTANT SAFETY INFORMATION (CONT)

Use of BRAFTOVI + MEKTOVI is associated with the following WARNINGS and PRECAUTIONS: New Primary Malignancies, Tumor Promotion in BRAF Wild-Type Tumors, Cardiomyopathy, Venous Thromboembolism, Hemorrhage, Ocular Toxicities, Interstitial Lung Disease, Hepatotoxicity, Rhabdomyolysis, QTc Prolongation, Embryo-Fetal Toxicity, Risks Associated with BRAFTOVI as a Single Agent. For more information, see **IMPORTANT SAFETY INFORMATION on pages 18-20**.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 18-20. Please see accompanying full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

Pfizer Oncology