AIM AT MELANOMA FOUNDATION | MELANOMA NURSING INITIATIVE

Encorafenib/Binimetinib Combination Therapy for Melanoma

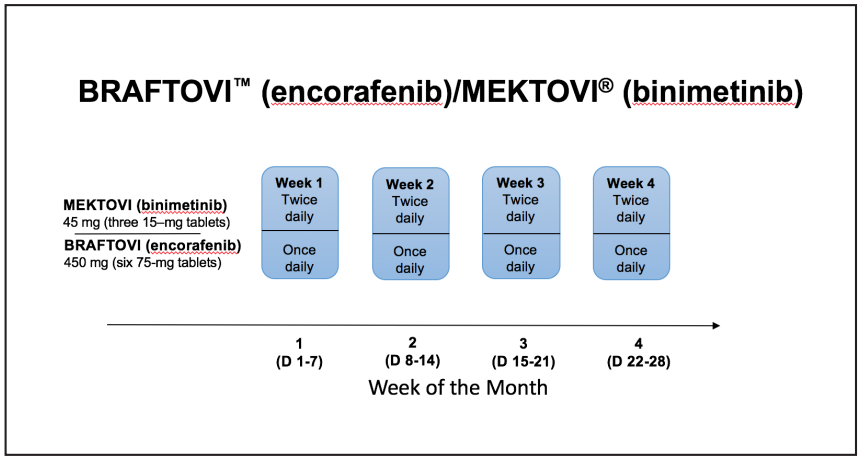
A Nursing Tool From The Melanoma Nursing Initiative (MNI)

Encorafenib (Braftovi™)/binimetinib (Mektovi®) combination therapy is indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation. Encorafenib is an inhibitor of some mutated forms of BRAF kinase, including *BRAF* V600E and V600K. About half of patients with melanoma have a mutated form of the BRAF protein in their tumor(s). Binimetinib is a MEK1 and MEK2 inhibitor. Combination BRAF/MEK inhibitor therapy is associated with superior tumor response and improved patient survival compared with single-agent BRAF inhibitor therapy (vemurafenib or encorafenib). This second-generation BRAF/MEK inhibitor combination, encorafenib/binimetinib, was developed to optimize pharmacologic properties in terms of improved efficacy (increased on-target activity) and tolerability (decreased off-target effects).

This document is part of an overall nursing toolkit intended to assist nurses in optimizing care of melanoma patients receiving newer anti-melanoma therapies.

DRUG DOSAGE/ADMINISTRATION

Both encorafenib and binimetinib are orally administered drugs. Binimetinib is administered as 45 mg (three 15-mg tablets) twice daily and encorafenib as 450 mg (six 75-mg capsules) once daily, each according to the regimens outlined below. The encorafenib dose can be taken at the same time as one of the binimetinib doses. The schedule repeats until disease progression or unacceptable toxicity develops.



- If the patient misses a dose of encorafenib or binimetinib, instruct patients as follows:
  - » Binimetinib: Do not take a missed dose if it is within 6 hours of when the next dose is due. Instead, wait and take the dose at the normal time
  - » Encorafenib: Do not take a missed dose if it is within 12 hours of when the next dose is due. Instead, wait and take the dose at the normal time
  - » A double dose of either binimetinib or encorafenib should NOT be taken to make up for a missed dose
  - » Do not take an additional dose of either binimetinib or encorafenib if vomiting occurs during or after administration. Continue with the next dose at the normal time

- Encorafenib and binimetinib may be administered with or without food. These medications do not require refrigeration (store them at room temperature)
- For patients with moderate (total bilirubin greater than 1.5 and less than or equal to 3 × ULN and any AST) or severe (total bilirubin levels greater than 3 × ULN and any AST) hepatic impairment, binimetinib should be dosed at 30 mg BID rather than 45 mg BID
- In general, strong or moderate CYP3A4 **inhibitors** should be avoided while taking encorafenib. If short-term concomitant use of a CYP3A4 inhibitor is unavoidable, **reduce** the encorafenib dosage to one third (eg, from 450 to 150 mg) for concomitant use with a strong inhibitor. Reduce the encorafenib dosage by half (eg, from 450 mg to 225 mg) for concomitant use with a moderate inhibitor. When discontinuing the CYP3A4 inhibitor, allow 3-5 elimination half-lives for the inhibitor before resuming encorafenib at the prior dose

The strong interactive potential of encorafenib with medications metabolized by CYP3A4 requires special consideration. Medication reconciliation is an essential and ongoing process. Oncology providers should work closely with the oncology pharmacist and primary care provider when evaluating medications used for other conditions—selecting agents with the least interaction potential and employing thorough documentation.

SIDE EFFECTS AND THEIR MANAGEMENT

- Possible treatment-related adverse effects (AEs) should be discussed with patients before initiation of encorafenib/binimetinib therapy. Patients should be informed of the importance of immediately reporting any health changes that may reflect a treatment-related AE
- The most common AEs associated with encorafenib/binimetinib were fatigue (experienced by 43% of patients in trials), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), and arthralgias (26%)

AEs associated with encorafenib/binimetinib therapy can be generally categorized into those that are most common (but typically mild to moderate in severity) and less common but serious or unique AEs. Table 1 shows the common and less common but serious or unique AEs associated with encorafenib/binimetinib as well as other AEs (Appendices 1 and 2).

Table 1. Guidance on management of adverse events associated with encorafenib/binimetinib

Category	Adverse Effect	Treatment Guidance (Appendix Number)
Most common (occurring in ≥15% of patients)	Fatigue	2
	Gastrointestinal	
	• Diarrhea	2
	• Nausea	2
	• Vomiting	2
	• Abdominal pain	2
	• Constipation	2
	Joint/muscle pain	
	• Arthralgias	2
	• Myopathy	2
	Skin disorders	1
	• Hyperkeratosis	1
	• Rash	1
	• Dry skin	1
	Headache	2
	Ocular toxicity	1
	• Visual impairment	1
	• Serous retinopathy/RPED	1
	Pyrexia	2
	Hemorrhage	2
	Dizziness	2

Table 1. Guidance on management of adverse events associated with encorafenib/binimetinib (Continued)

Category	Adverse Effect	Treatment Guidance (Appendix Number)
Less common (≤10%) but serious or unique to BRAF/MEK inhibitors	New primary cancers (cutaneous and noncutaneous)	1
	Cardiovascular	
	• Cardiomyopathy (reduced LVEF)	1
	• Venous thromboembolism (pulmonary embolism, deep vein thrombosis)	2
	• QTc prolongation	1
	Drug hypersensitivity	2
	Facial paresis	2
	Hepatotoxicity	2
	Interstitial lung disease/pneumonitis	2
	Pancreatitis	2
	Panniculitis	2
	Pyrexia	2
	Rhabdomyolysis	2
	Uveitis	1

Severe and sometimes moderate AEs are commonly managed by dose interruptions or withdrawal (Table 2). In certain cases, referral to a specialty care (e.g., cardiology, dermatology, or ophthalmology) specialist is warranted.

Table 2. Recommended Dosage Reductions for Encorafenib/Binimetinib*

Encorafenib	Dosage Reduction From 450 mg Orally Once Daily to
First dose reduction	300 mg orally once daily
Second dose reduction	200 mg orally once daily
Subsequent modification	Permanently discontinue if unable to tolerate 200 mg once daily
Binimetinib	**Dosage Reduction From 45 mg Orally Twice Daily to**
First dose reduction	30 mg orally twice daily
Subsequent modification	Permanently discontinue if unable to tolerate 30 mg twice daily

*If binimetinib is held for any reason, the dose of encorafenib should be reduced to 300 mg or less until binimetinib is resumed. In addition, when administered with binimetinib, dosage modification of encorafenib is not needed for new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; cardiac dysfunction; creatine phosphokinase (CPK) elevation; rhabdomyolysis; and venous thromboembolism.

CLINICAL PEARLS

- Before beginning targeted therapy, patients who previously received immunotherapy should be monitored carefully for possible overlapping toxicities. Several AEs are observed with both targeted therapy and immunotherapy and may result in cumulative toxicities
- Potential drug-drug interactions are an important component of encorafenib/binimetinib therapy
  - » In addition to interactions with CYP3A4 inhibitors/inducers, encorafenib may adversely interact with other drugs to prolong the QT interval. It is important to identify these medications so they are not used concomitantly and/or drug dosages are appropriately modified
  - » For patients of childbearing age, contraception should be used during treatment and for 30 days after the last dose of the combination. Women should use an effective, nonhormonal method of contraception because encorafenib can render hormonal contraceptives ineffective
  - » Patients should be encouraged to have all their medications filled by a single pharmacy to ensure familiarity with the full medication list and to avoid polypharmacy issues
- Patients should be seen by a dermatologist before beginning treatment, every 2 months during treatment, and as long as 6 months after treatment discontinuation
- Because of the potential for cardiomyopathy, assess left ventricular ejection fraction (LVEF) before treatment initiation, after 1 month of treatment, then every 2 to 3 months during treatment. The safety of binimetinib has not been established in patients with LVEF below 50% or below the institutional lower limit of normal. Patients with cardiovascular risk factors should be monitored closely when treated with binimetinib
- New skin cancers often initially present as a new wart, skin sore, a reddish bump that bleeds or does not heal, and/or as a change in size or color of a mole. Patients should be made aware of this association and advised to immediately report any skin changes to the healthcare team
- Advise patients to take pictures of any skin changes for documentation
- Use caution if switching to encorafenib/binimetinib from another BRAF/MEK inhibitor combination regimen due to intolerable pyrexia, as recurrent pyrexia may occur
- Some patients develop acute-onset vision changes within 12 to 36 hours of starting the combination encorafenib/binimetinib. This is usually a transient effect associated with binimetinib. However, if the vision changes do not resolve in a day or so, further evaluation is warranted. It is important to inform patients about this potential early side effect and the importance of careful monitoring
- Unique to this BRAF/MEK inhibitor combination, the BRAFi (encorafenib) is administered ONCE daily, while the MEKi (binimetinib) is administered TWICE daily

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QUESTIONS & ANSWERS

Q. Patients often ask me how to tell if the medication is working. What can I tell them?

A. You can advise patients that the oncology team will be seeing them on a regular basis, to perform a physical exam, assess for symptoms, and review labs. In addition, the team will perform restaging scans every 8–12 weeks to assess response to therapy.

Ask your patients to keep a diary of their symptoms and possible adverse effects that they might be experiencing with this therapy. Tell them that they may also notice certain symptoms, such as pain starting to lessen, which could mean that their tumor(s) is/are starting to shrink.

Q. If binimetinib needs to be held for any reason, how should the encorafenib dosage be adjusted?

A. When binimetinib is held, the encorafenib dosage should be reduced to 300 mg daily or less until binimetinib is resumed. This is because encorafenib, when given alone, is associated with an increased risk of certain adverse events (such as dermatologic reactions) than when given together with binimetinib.

Q. How long will patients stay on BRAF/MEK inhibitor therapy?

A. Most likely, patients will continue therapy as long as their disease is responding and they are tolerating the treatment. During the clinical trials, treatment was discontinued for disease progression or intolerable toxicity not managed with drug holidays or dose reduction.

QUESTIONS & ANSWERS

Continued

Q. Which cutaneous malignancies should we monitor for?

A. Use of BRAF inhibitors has been associated with new primary malignancies. New primary cutaneous malignancies include squamous cell carcinomas (and a variant known as keratoacanthomas), basal cell carcinomas, and new primary melanomas. In the Columbus trial, cutaneous squamous cell carcinomas/keratoacanthomas occurred in 2.6% of patients, while basal cell carcinomas occurred in 1.6% of patients who received encorafenib in combination with binimetinib. The median time to first occurrence of cutaneous squamous cell carcinoma/keratoacanthomas was 5.8 months.

For these reasons, dermatologic evaluations are recommended prior to treatment initiation, every 2 months during treatment, and for up to 6 months following discontinuation of treatment with encorafenib/binimetinib. Sun damaged skin (e.g., head and neck, hands) is a common location for new cutaneous malignancies to occur. Squamous cell carcinomas commonly appear as scaly red patches or ulcerated lesions with elevated borders and a central depression. Keratoacanthomas are typically dome-shaped, symmetrical, volcano-like lesions surrounded by a smooth wall of inflamed skin, with a cap of keratin scales and debris. Suspicious lesions should be excised with dermatopathologic evaluation. Dose modification is not necessary for new primary cutaneous malignancies.

Q. How do I access binimetinib + encorafenib for my patients?

A. The Fact Sheet contains information about ordering and dispensing binimetinib and encorafenib, including a list of select specialty pharmacies that carry the combination. The Fact Sheet also provides information about enrolling patients in the Array ACTS™ program, which helps with medication access, regardless of insurance coverage. The Fact Sheet is available at https://www.braftovimektovi.com/wp-content/uploads/Ordering_fact-sheet.pdf

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PATIENT RESOURCES

Financial Assistance

Array ACTS™
1-866-ARRAYCS (1-866-277-2927)
http://www.braftovimektovi.com/patient/savings-and-support/

Additional Information Resources

AIM at Melanoma Foundation (Nurse on Call, patient symposia, drug resources, etc)
http://www.AIMatMelanoma.org

American Cancer Society: Targeted therapy for melanoma skin cancer
https://www.cancer.org/cancer/melanoma-skin-cancer/treating/targeted-therapy.html

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ADDITIONAL RESOURCES

- Czupryn M, Cisneros J. BRAF/MEK inhibitor therapy: consensus statements from the faculty of the Melanoma Nursing Initiative on managing adverse events and potential drug interactions. *Clin J Oncol Nurs*. 2017;21(suppl):11-29.
- Davis ME. Ocular toxicity of tyrosine kinase inhibitors. *Oncol Nurs Forum*. 2016;43:235-243. doi:10.1188/16.ONF.235-243
- de Golian E, Kwong BY, Swetter SM, Pugliese SB. Cutaneous complications of targeted melanoma therapy. *Curr Treat Options Oncol*. 2016;17:57. doi:10.1007/s11864-016-0434-0
- 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;19:603-615.
- Koelblinger P, Theurigen O, Dummer R. Development of encorafenib for BRAF-mutated advanced melanoma. *Curr Opin Oncol*. 2018;30:125-133.
- Mavropoulos JC, Wang TS. Managing the skin toxicities from new melanoma drugs. *Curr Treat Options Oncol*. 2014;15:281-301.
- Rubin KM. Care and management of unique toxicities associated with MAPK pathway-targeted therapies in patients with advanced melanoma. *Clin J Oncol Nurs*. 2017;21:699-709.
- Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol.* 2015;7:122-136.

Click here for downloadable action plans to customize for your patients

APPENDIX 1

The CSPs for skin toxicity, cardiotoxicity, and ocular toxicities referenced here are housed in the CSP section of the MNI website (TheMelanomaNurse.org). They contain information for all the BRAF/MEK inhibitors.

Please click the link below to access the CSPs, which can also be printed from the site:

http://themelanomanurse.org/care-step-pathways/

APPENDIX 2

Detection and management of AEs and laboratory abnormalities not included in care step pathways for encorafenib/binimetinib.

Adverse event	Common symptoms	Common management/anticipatory guidance
Arthralgias/myalgias	Joint pain swelling or stiffness; feeling tired; loss of strength	• Query patients regarding joint symptoms; standard supportive care (analgesia and anti-inflammatory drugs) • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (moderate pain, limiting instrumental ADLs) or first occurrence of Grade 3 (severe pain and self-care ADL limitations) • Permanently discontinue or withhold binimetinib and encorafenib for Grade 4 (life-threatening consequences); resume when AE resolves to Grade 0-1; permanently discontinue binimetinib and encorafenib for recurrent Grade 3 or Grade 4 • Obtain referral to rheumatology to minimize the chance of permanent joint damage
Colitis	Abdominal pain/ tenderness, blood or mucus in stool, bloating	• Evaluate for infectious, non-infectious, and disease-related causes • Patients who have developed diarrhea or colitis with prior immunotherapy require close monitoring • Standard supportive therapy: bland diet, support hydration • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (abdominal pain; blood or mucus in stool; limiting instrumental ADLs) or first occurrence of Grade 3 (severe abdominal pain; peritoneal signs of tenderness, pain, bloating) • Permanently discontinue or withhold binimetinib and encorafenib for Grade 4 (life-threatening consequences such as hemodynamic collapse); resume when AE resolves to Grade 0-1; permanently discontinue binimetinib and encorafenib for recurrent Grade 3 or Grade 4
Constipation/ abdominal pain	Infrequent stools/ difficulty stooling, abdominal pain	• Increase fluid, fiber, laxatives. Consider appropriate testing to evaluate for bowel obstruction • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (persistent symptoms of constipation or moderate pain limiting instrumental ADLs) or first occurrence of Grade 3 (constipation with manual evacuation indicated, severe abdominal pain) • Permanently discontinue or withhold binimetinib and encorafenib for Grade 4 (life-threatening consequences); resume when AE resolves to Grade 0-1; permanently discontinue binimetinib and encorafenib for recurrent Grade 3 or Grade 4

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Detection and management of AEs and laboratory abnormalities not included in care step pathways for encorafenib/binimetinib.

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Adverse event	Common symptoms	Common management/anticipatory guidance
Diarrhea	Loose, watery stools; increased frequency and urgency	• Evaluate for infectious, non-infectious, and disease-related causes • Standard supportive therapy; bland diet; support hydration • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (increase of 4-6 stools/day over baseline; increased ostomy; limiting instrumental ADLs) or first occurrence of Grade 3 (increase of ≥7 stools/day over baseline; incontinence; severe increase in ostomy output over baseline; limiting self-care ADLs) • Permanently discontinue or withhold binimetinib and encorafenib for Grade 4 (life-threatening consequences); resume when AE resolves to Grade 0-1; permanently discontinue binimetinib and encorafenib for recurrent Grade 3 or Grade 4
Edema	Swelling of limbs, etc	• Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (moderate swelling; limiting instrumental ADLs) or first occurrence of Grade 3 (severe swelling, gross deviation from anatomic contour) • Permanently discontinue binimetinib and encorafenib for recurrent Grade 3
Embryo-Fetal Toxicity	----------	• Binimetinib and encorafenib can cause fetal harm. Females and males of child-bearing potential should use effective, nonhormonal birth control during encorafenib/binimetinib treatment and for at least 30 days after the final dose of encorafenib/binimetinib
Facial paresis	Face muscles appear to droop or become weak; can be bilateral or unilateral	• Rule out infectious, non-infectious, and disease-related causes • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (moderate symptoms; limiting instrumental ADLs) or first occurrence of Grade 3 (severe symptoms; limiting self-care ADLs) • Permanently discontinue binimetinib and encorafenib for recurrent Grade 3
Fatigue	Unrelenting exhaustion not relieved by rest	• Query patients regarding energy level; rule out other causes, including infection, disease progression, and hematological and biochemical abnormalities; standard supportive care • Withhold binimetinib and encorafenib for recurrent fatigue not relieved by rest (and limiting instrumental ADLs, Grade 2) and the first occurrence of Grade 3 (severe symptoms, limiting self-care ADLs) • Permanently discontinue binimetinib and encorafenib for recurrent Grade 3

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Detection and management of AEs and laboratory abnormalities not included in care step pathways for encorafenib/binimetinib.

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Adverse event	Common symptoms	Common management/anticipatory guidance
Headache	Pain and/or change in vision	• May be multifactorial. For severe symptoms, could involve bleeding in the brain, uncontrolled hypertension, dehydration, new CNS disease, or other causes; consider brain MRI and evaluate for hypertension • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (moderate pain; limiting instrumental ADLs) or first occurrence of Grade 3 (severe pain; limiting self-care ADLs) • Permanently discontinue binimetinib and encorafenib for recurrent Grade 3
Hemorrhage	Red or black/tarry stools, blood in urine, headaches, coughing or vomiting blood, abdominal pain, unusual vaginal bleeding, fatigue, dizziness, or weakness	• Standard supportive care; medical intervention as indicated • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (moderate bleeding) or first occurrence of Grade 3 (severe bleeding requiring transfusion or radiologic, endoscopic, or operative intervention) • Permanently discontinue or withhold binimetinib and encorafenib for Grade 4 (life-threatening consequences); resume when AE resolves to Grade 0-1; permanently discontinue binimetinib and encorafenib for recurrent Grade 3 or Grade 4
Hepatotoxicity	Abdominal pain or swelling; yellowing of skin or eyes; dark urine; easy bruising; loss of appetite; feeling tired or weak	• Monitor LFTs at baseline and monthly during treatment or as clinically indicated • Evaluate for other causes such as concomitant medications (both prescribed and OTC as well as supplements and herbals), infectious etiologies, as well as disease progression • Withhold binimetinib at first occurrence of Grade 3/4 (transaminases or alkaline phosphatase >5× ULN, bilirubin >3× ULN) and permanently discontinue if not improved within 4 weeks • Withhold binimetinib for Grade 2 AST or ALT increase (transaminases >3× ULN, alkaline phosphatase >2.5× ULN, or bilirubin >1.5× ULN) if no improvement within 2 weeks; then after improved to Grade 0/1 or pretreatment/baseline levels, resume at the same dosage • Withhold encorafenib for persistent (more than 4 weeks) Grade 2 (transaminases >3 × ULN, alkaline phosphatase >2.5× ULN, or bilirubin >1.5× ULN) until improves to Grade 0/1; resume at same dosage • Withhold encorafenib for Grade 3/4 (transaminases or alkaline phosphatase >5× ULN, bilirubin >3× ULN) and permanently discontinue if no recovery to Grade 0/1 within 4 weeks or for recurrent Grade 4 event

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Detection and management of AEs and laboratory abnormalities not included in care step pathways for encorafenib/binimetinib.

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Adverse event	Common symptoms	Common management/anticipatory guidance
Hypersensitivity reaction	Swelling, feeling faint, rash, erythema, anaphylaxis	• Possible hospitalization depending on severity • Immediate permanent discontinuation of encorafenib for patients with severe hypersensitivity reactions
Interstitial lung disease/pneumonitis	Shortness of breath, cough, fatigue; difficulty ambulating	• Assess for other etiologies such as infection, pulmonary embolism, progressive lung metastases, pleural effusion, or lung disease • Assess pulse oximetry and consider chest CT or X-ray • Withhold binimetinib for 4 weeks for Grade 2 (symptomatic; limiting instrumental ADLs); if improved to Grade 0/1, resume at reduced dose; if not resolved within 4 weeks, permanently discontinue binimetinib • Permanently discontinue binimetinib for Grade 3/4 (severe symptoms; limiting self-care ADLs; oxygen indicated or life-threatening respiratory compromise requiring tracheostomy/intubation) • WIthhold encorafenib for up to 4 weeks for recurrent Grade 2 or first occurrence of Grade 3; permanently discontinue or withhold encorafenib for Grade 4; resume when AE resolves to Grade 0/1 • Permanently discontinue encorafenib for recurrent Grade 3 or Grade 4
Nausea/vomiting	Vomiting, queasiness, RUQ or LUQ pain	• May indicate hepatotoxicity, CNS metastasis; check LFTs/lipase/amylase; provide standard supportive care • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (oral intake decreased or 3-5 vomiting episodes in 24 hours) or first occurrence of Grade 3 (inadequate intake or ≥6 vomiting episodes in 24 hours) • Permanently discontinue or withhold binimetinib and encorafenib for Grade 4 (life-threatening consequences); resume when AE resolves to Grade 0/1; permanently discontinue binimetinib and encorafenib for recurrent Grade 3 or Grade 4
Pancreatitis	Upper abdominal pain; fever, rapid pulse, nausea, vomiting, abdominal tenderness	• Rule out infectious, non-infectious, or disease-related causes • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (symptomatic; limiting instrumental ADLs) or first occurrence of Grade 3 (severe symptoms; limiting self-care ADLs) • Permanently discontinue or withhold binimetinib and encorafenib for Grade 4 (life-threatening consequences); resume when AE resolves to Grade 0/1 • Permanently discontinue binimetinib and encorafenib for recurrent Grade 3 or Grade 4

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Detection and management of AEs and laboratory abnormalities not included in care step pathways for encorafenib/binimetinib.

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Adverse event	Common symptoms	Common management/anticipatory guidance
Pyrexia	Elevated temperature, chills/rigors	• Standard supportive care • Evaluate previous treatments and any history of pyrexia (could be recurrent) • Withhold binimetinib and encorafenib for up to 4 weeks for recurrent Grade 2 (fevers 101.3°F–104.0°F [38.5°C–40.0°C]; mildly symptomatic, affecting instrumental ADLs) or first occurrence of Grade 3 (fevers >104.0°F [40.0°C] or 101.3°F–104.0°F [38.5°C–40.0°C] that is moderately symptomatic, limiting self-care ADLs) • Permanently discontinue or withhold binimetinib and encorafenib for Grade 4 (any fever that is highly symptomatic [acute renal insufficiency, hypotension requiring hospitalization. life-threatening consequences]); resume when AE resolves to Grade 0/1 • Permanently discontinue binimetinib and encorafenib for recurrent Grade 3 or Grade 4
Rhabdomyolysis	Pain, muscle weakness, vomiting, confusion, tea-colored urine	• Check serum creatine phosphokinase (CPK) levels • Intravenous fluids and other supportive therapy • Depending on the clinical situation, withhold binimetinib or encorafenib for 4 weeks for any Grade 4 asymptomatic CPK elevation (>10x ULN) or any grade CPK elevation with symptoms or with renal impairment. Resume when AE resolves to Grade 0/1; if not resolved in 4 weeks, permanently discontinue binimetinib and encorafenib
Venous thromboembolism	Pain, swelling, redness, warmth near a deep vein thrombosis in a limb Chest pain, fast heart rate, difficulty breathing, dizziness or loss of consciousness	• D-dimer test; imaging tests, including CT scan or ventilation/perfusion scan • Withhold binimetinib and encorafenib for uncomplicated deep vein thrombosis or pulmonary embolism; if no improvement to Grade 0/1, permanently discontinue binimetinib • Depending on the situation, for life-threatening (Grade 4) pulmonary embolism, permanently discontinue binimetinib and encorafenib