Cobimetinib/vemurafenib combination therapy is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. Cobimetinib is a MEK1 and MEK2 inhibitor, and vemurafenib is an inhibitor of some mutated forms of BRAF kinase, including BRAF V600E. About half of patients with melanoma have a mutated form of the BRAF protein in their tumors. Combination MEK/BRAF inhibitor therapy is associated with superior tumor response and improved patient survival compared with single-agent BRAF inhibitory therapy. Using the combination also decreases the high rates of secondary cutaneous malignancies associated with single-agent BRAF inhibitory therapy.

This document is part of an overall nursing toolkit intended to assist nurses in optimizing care of melanoma patients receiving newer anti-melanoma therapies.
For advanced melanoma, both cobimetinib and vemurafenib are orally administered drugs. Cobimetinib is administered as 60 mg (three 20-mg tablets) once daily for a total of 1920 mg, each according to the regimens outlined below. The schedule repeats until disease progression or unacceptable toxicity occurs.

- Cobimetinib: If ≤4 hours from scheduled dosing time, take the dose. If >4 hours, hold that dose and take the next scheduled dose at the normal time.
- Vemurafenib: A missed dose can be taken up to 4 hours prior to the next dose. If >4 hours, hold that dose and take the next scheduled dose at the normal time.
- If the patient misses a dose of cobimetinib or vemurafenib, adjust as follows:
  - Cobimetinib: If ≤4 hours from scheduled dosing time, take the dose. If >4 hours, hold that dose and take the next scheduled dose at the normal time.
  - Vemurafenib: A double dose of either cobimetinib or vemurafenib should be taken to make up for a missed dose.

In general, strong or moderate CYP3A4 inhibitors should be avoided while taking vemurafenib. If short-term concomitant use of a moderate CYP3A4 inhibitor is unavoidable, reduce the vemurafenib dose from 960 mg (four 240-mg tablets) twice daily to 720 mg (three 240-mg tablets) twice daily. After discontinuation of the CYP3A4 inhibitor, resume the previous dose of vemurafenib.

Vemurafenib tablets should not be crushed or chewed. For advanced melanoma, both cobimetinib and vemurafenib are orally administered drugs. Cobimetinib is administered as 60 mg (three 20-mg tablets) once daily for 3 weeks, followed by a 1-week break, and vemurafenib as 960 mg (four 240-mg tablets) twice daily. For advanced melanoma, both cobimetinib and vemurafenib are orally administered drugs. Cobimetinib is administered as 60 mg (three 20-mg tablets) once daily for 3 weeks, followed by a 1-week break.
• Possible treatment-related adverse events (AEs) should be discussed with patients before initiation of cobimetinib/vemurafenib therapy. Patients should be informed of the importance of immediately reporting any health changes that may reflect a treatment-related AE.

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

### Table 1. AEs Associated With Cobimetinib/Vemurafenib

<table>
<thead>
<tr>
<th>irAE category</th>
<th>Examples</th>
<th>Treatment guidance (Appendix number)</th>
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<tbody>
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SIDE EFFECTS AND THEIR MANAGEMENT (CONTINUED)

- Severe and sometimes moderate AEs are commonly managed by dose interruptions or withdrawal. In certain cases, referral to a cardiology, dermatology, or ophthalmology specialist is warranted.

### Table 2: Recommended Dose Reductions for Cobimetinib/Vemurafenib

<table>
<thead>
<tr>
<th>Cobimetinib</th>
<th>Dose Reduction From 60 mg Orally Once Daily To</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose reduction</td>
<td>40 mg orally once daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>20 mg orally once daily</td>
</tr>
<tr>
<td>Subsequent modification</td>
<td>Permanently discontinue if unable to tolerate 20 mg once daily</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Dose Reduction From 960 mg Orally Twice Daily To</td>
</tr>
<tr>
<td>First dose reduction</td>
<td>720 mg orally twice daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>480 mg orally twice daily</td>
</tr>
<tr>
<td>Subsequent modification</td>
<td>Permanently discontinue if unable to tolerate 480 mg twice daily</td>
</tr>
</tbody>
</table>
Before beginning targeted therapy, patients who previously received immunotherapy should be monitored carefully for possible overlapping toxicities. Several AEs are observed with both targeted and immunotherapy and may result in cumulative toxicities.

Potential drug-drug interactions are an important component of cobimetinib/vemurafenib therapy for melanoma.

- In addition to interactions with CYP3A4 inhibitors/inducers, cobimetinib/vemurafenib 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 drugs doses are appropriately modified.

- 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 many as 7 months after treatment discontinuation.

New skin cancers often initially present as a new wart, skin sore or 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 lesions for documentation.
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, usually at least monthly, to perform a physical exam and review the labs and symptoms. In addition, your team will perform restaging scans every 8–12 weeks to assess response to therapy. A member of the oncology team will be ordering a LDH level, which is a lab test that acts as a marker for melanoma and can help assess the patient’s response to treatment.

Ask your patients to keep a diary of their symptoms and possible adverse events that they might be experiencing with this therapy. Tell the patients 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. How long will patients stay on BRAF/MEK inhibitor therapy?

A. Most likely, patients will continue therapy if their disease is responding to therapy and they are tolerating the side effects. During the clinical trials, the patients who had to stop therapy were those who had disease progression or had moderate to severe drug toxicities that affected their quality of life and required persistent drug holidays, dose reduction, or discontinuation.
PATIENT RESOURCES

Financial Assistance
Cotellic and Zelboraf Access Solutions
888-249-4918
http://www.genentech-access.com/cotellic/patients

COTELLIC® (cobimetinib)/ZELBORAF® (vemurafenib)
Information Resources
For more information about this therapy and support:
Nursing Hotline
855-MY-COTELLIC (855-692-6835)

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
ADDITIONAL RESOURCES


Click here for downloadable action plans to customize for your patients
Pyrexia

**Care Step Pathway - Pyrexia**

( elevated body temperature in the absence of clinical or microbiological evidence of infection)

**Grading Toxicty**

- **Grade 1 (Mild)**

- **Grade 2 (Moderate)**

- **Grade 3 (Severe)**

- **Grade 4 (Potentially Life-Threatening)**

**Symptoms Suggestive of Infections**

- Painless lymphadenopathy

- Power fatigue requiring hospitalization

**Recent International or National Travel?**

- Yes

- No

**Recent Exposure to Animals?**

- Yes

- No

**Recent Sick Contacts?**

- Yes

- No

**Symptoms Suggestive of Infection**

- New or worsening symptoms

- Unusual fever

- Unusual rash

- Unusual cough

**Impact of Symptoms on QoL or Performance**

- Yes

- No

**Potential Infectious Causes (via urinalysis, urine cultures, throat cultures, blood cultures, etc)**

- Yes

- No

**Adequacy of Fluid Intake in the Last 24 Hours (How Much, Types, etc)**

- Yes

- No

**Does the Patient Appear Dehydrated?**

- Yes

- No

**Does the Patient Appear Unwell?**

- Yes

- No

**Does the Patient Appear Deteriorated?**

- Yes

- No

**Does the Patient Appear Death**

- Yes

- No

**Recent International or National Travel?**

- Yes

- No

**Recent Exposure to Animals?**

- Yes

- No

**Recent Sick Contacts?**

- Yes

- No

**Symptoms Suggestive of Infection**

- New or worsening symptoms

- Unusual fever

- Unusual rash

- Unusual cough

**Impact of Symptoms on QoL or Performance**

- Yes

- No

**Potential Infectious Causes (via urinalysis, urine cultures, throat cultures, blood cultures, etc)**

- Yes

- No

**Adequacy of Fluid Intake in the Last 24 Hours (How Much, Types, etc)**

- Yes

- No

**Does the Patient Appear Dehydrated?**

- Yes

- No

**Does the Patient Appear Unwell?**

- Yes

- No

**Does the Patient Appear Deteriorated?**

- Yes

- No

**Does the Patient Appear Death**

- Yes

- No

**Care Step Pathway - Pyrexia**

- Assess patient & family understanding of recommendations and rationale

- Identify barriers to adherence

- Assess for potential drug-drug interactions

- Determine if concomitant medications contain antipyretics

- Increase oral hydration to minimize insensible losses. Suggested fluids: water, juice, sports drinks (e.g., Gatorade, Powerade), popsicles

- Prompt medical and supportive care interventions

- Aggressive hydration management to address hypotension, etc

- Acetaminophen or ibuprofen q4-6hrs until fever resolves

- Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen

- For pyrexia refractory to antipyretics, CS with prednisone or equivalent will be used, 25 mg/d, with downward titration; consider change in targeted therapy, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib if fever persists)

- For recurrent pyrexia, CS with prednisone or equivalent will be used (10 mg/day for at least 5 days); consider change in targeted therapy, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib if fever persists)

- Change to different targeted therapy regimen, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib if fever persists)

- Acetaminophen or ibuprofen q4-6hrs until fever resolves (<99°F [37.2°C]) for 24 hours, possible treatment restart with appropriate dose

- For fevers >104°F (>40.0°C) that is moderately symptomatic (rigors, chills, etc) or threatens life or there is other clinical concern. Set hydration goals

- Intravenous, as needed

- Grade 1 (Mild)

- Grade 2 (Moderate)

- Grade 3 (Severe)

- Grade 4 (Potentially Life-Threatening)

- Pyrexia Page 1 of 2


**Management**

- Identify barriers to adherence
- Assess patient and family understanding of recommendations and ADLs
- Assess recent history of febrile episodes:
  - Previous (e.g., upper respiratory, urinary, etc.)
  - Recent international or national travel?
  - Recent sick contacts?
  - Symptoms suggestive of infectious etiology (e.g., upper respiratory, urinary, etc.)
  - Potential infectious causes (via urinalysis, urine cultures, throat cultures, blood cultures, etc.)
  - Adequacy of fluid intake in the last 24 hours (how much, types, etc.)

- Grade of fever and chills if present
- Impact of symptoms on QoL/performance
- Recognize:
  - Other symptoms, such as dehydration, rigors, hypotension, malaise, fatigue, GI or respiratory symptoms
  - Other treatment-related adverse events

- Recognize:
  - Pale?
  - Hypotension requiring hospitalization, prompt management

- Review medication profile with patient and family
- Include potential drug-drug interactions
- Is the patient currently febrile?
- Does the patient appear unwell?
- Does the patient appear dehydrated?

- Grade 1 (Mild)
  - Asymptomatic; mild, low-grade fever
  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen
  - Do not exceed 400 mg/d acetaminophen or ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours
  - For temperatures >101.3°F (38.5°C), dabrafenib to be held (Grade 3) or discontinued (Grade 4)
  - For fevers >104°F (>40.0°C), or any fever accompanied by chills, fever of 101.3°F–104.0°F (38.5°C–40.0°C) that is moderately symptomatic (chills, etc)

- Grade 2 (Mild to Moderate)
  - Moderate: causing moderate changes in the patient’s status (e.g., if dabrafenib is held for 4 days)
  - Hypotension; limiting self-care
  - Fever of 101.3°F–104.0°F (38.5°C–40.0°C); mildly symptomatic (rigors, chills, etc)
  - For recurrent pyrexia, CS with prednisone or equivalent will be used (10 mg/day for at least 5 days);
    consider change in targeted therapy regimen, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib if fever persists)
  - For recurrent pyrexia, CS with prednisone or equivalent will be used, 25 mg/d, with downward titration; consider change in targeted therapy, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib)
  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen
  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours
  - Possible treatment restart with appropriate dose

- Grade 3 (Severe)
  - Severe: causing severe changes in the patient’s status (e.g., if dabrafenib is held for 7 days)
  - Hypotension requiring hospitalization, prompt management
  - Fever of 101.3°F–104.0°F (38.5°C–40.0°C); moderately symptomatic (acute renal insufficiency, hypotension requiring hospitalization, prompt management)
  - For temperatures >101.3°F (38.5°C), dabrafenib to be held (Grade 3) or discontinued (Grade 4)
  - For fevers >104°F (>40.0°C), or any fever accompanied by chills, fever of 101.3°F–104.0°F (38.5°C–40.0°C) that is moderately symptomatic (rigors, chills, etc)
  - For recurrent pyrexia, CS with prednisone or equivalent will be used (10 mg/day for at least 5 days);
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  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours
  - Possible treatment restart with appropriate dose

- Grade 4 (Potentially Life Threatening)
  - Potentially life-threatening, if clinical deterioration occurs
  - Severe hypotension; limiting self-care
  - Fever of 101.3°F–104.0°F (38.5°C–40.0°C); highly symptomatic (rigors, chills, etc)
  - For recurrent pyrexia, CS with prednisone or equivalent will be used (10 mg/day for at least 5 days);
    consider change in targeted therapy regimen, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib if fever persists)
  - For recurrent pyrexia, CS with prednisone or equivalent will be used, 25 mg/d, with downward titration; consider change in targeted therapy, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib)
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  - Possible treatment restart with appropriate dose

- Self-management of fevers (OTC agents, medications, tepid baths)
- Care Step Pathway
- Grade 2 (Severe or Potentially Life Threatening)
  - Use tepid baths
  - Acetaminophen or ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours
  - Intravenous, as needed
  - Oral, advise fluids: water, rehydration drinks (Pedialyte®), juice, sports drinks (Gatorade®, Powerade®), popsicles
  - Increase oral hydration to minimize insensible losses. Suggested fluids: water, juice, sports drinks (Gatorade®, Powerade®, Pedialyte®)
  - Hospitalization, if clinically indicated
  - Monitor renal and hepatic function during antipyretic treatment

- Management of severe acute kidney injury
  - Acetaminophen or ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours
  - Hospitalization, if clinically indicated
  - Monitor renal and hepatic function during antipyretic treatment
  - Grade 1 (Mild)
  - Asymptomatic; mild, low-grade fever
  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen
  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours

- Management of fever
  - Acetaminophen or ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours
  - Intravenous, as needed
  - Oral, advise fluids: water, rehydration drinks (Pedialyte®), juice, sports drinks (Gatorade®, Powerade®), popsicles
  - Increase oral hydration to minimize insensible losses. Suggested fluids: water, juice, sports drinks (Gatorade®, Powerade®, Pedialyte®)
Management

Overall Strategy:
- Overall Strategy:
  - No change to therapy or intervention; wait for resolution
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  - No change to therapy or intervention; wait for resolution
  - No change to therapy or intervention; wait for resolution

Intervention (at-risk patients):
- Interventions at risk of superinfection
  - Interventions at risk of superinfection
  - Interventions at risk of superinfection
  - Interventions at risk of superinfection

ADL = activities of daily living; BSA = body surface area; QOL = quality of life

Concern for superinfection:
- Oral involvement
- Skin sloughing
- Extensive rash (>50% BSA), or rapidly progressive

Rash: consider topical antibiotic (clindamycin gel) if indicated
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Provocative measures:
- Provocative measures:
  - Provocative measures:
  - Provocative measures:
  - Provocative measures:

Potential Life Threatening (Grade 5)
- Potential Life Threatening (Grade 5)
- Potential Life Threatening (Grade 5)
- Potential Life Threatening (Grade 5)
- Potential Life Threatening (Grade 5)

Definition: A disorder characterized by an intense itching sensation.

PRURITUS

Grading
- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Potentially Life-Threatening)

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Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Maculopapular rash

RASH (maculopapular rash, acneiform rash, or dermatitis)

Grading
- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Potentially Life-Threatening)

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- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Potentially Life-Threatening)
Ocular Toxicity - Ocular Toxicity

Grading Toxicity (Overall, Ocular Toxicity)

Grade 4 (Severe)
- Severe vision changes, vision loss, marked decrease in visual acuity
- Symptoms: pain, floaters, photophobia, diplopia
- Signs: ptosis, miosis, pupillary reaction to light
- Need for urgent evaluation (treatment indicated)

Grade 3 (Moderate)
- Moderate vision changes, mild decrease in visual acuity
- Symptoms: pain, floaters, photophobia
- Signs: ptosis, miosis, pupillary reaction to light

Grade 2 (Mild)
- Mild vision changes, no decrease in visual acuity
- Symptoms: mild photophobia, mild floaters
- Signs: normal pupils, normal reactive to light

Assessing for permanent loss of vision
- Patient is unable to perform regular ADLs because of ocular issues
- Sudden vision disturbances such as photosensitivity, eye pain, and redness

Obtain ophthalmology clearance prior to restarting therapy for other moderate ocular toxicities, per prescribing information.

Assess adherence to eye drops/topical therapy.

Anticipate permanent discontinuation of targeted therapy for other severe ocular toxicities, per prescribing information.

Reduce dose or discontinue if no improvement after 3 weeks. Assess adherence to eye drops/topical therapy.

Specific targeted therapy dose
- Specific targeted therapy drug

In general, anticipate referral to ophthalmology.

Support adherence to eye drops/topical therapy.

Berpotentinaly Life-Threatening (20/20 or worse in affected eye(s))
- Blindness (20/200 or worse in affected eye(s))
- Severe vision changes (potentially life threatening)

Nursing Assessment

Care Step Pathway - Ocular Toxicity

Recognize

Listen

Look

Identify and closely monitor at-risk patients (including those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration)

Advise patients to promptly report any changes in vision or any eye symptoms (and anticipate treatment hold pending further evaluation)

If contact lenses are worn, advise patients to be meticulous about eye hydration, lens hygiene, and not using lenses beyond their disposal time

Identify and closely monitor at-risk patients (including those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration)

Promote good control of blood glucose since it reduces risk of retinal disease

Promote good hand hygiene

Encourage use of sunglasses and reduction in sun exposure

Smoking cessation, control of comorbidities

Diet (potentially including dietary supplements containing omega-3 and omega-6 fatty acids for dry eye syndrome)

Follow:

- Photophobia (oversensitivity to light): sunglasses, dim lights
- Conjunctivitis (inflammation of the interior eyelids): antihistamines, CS, cool compresses, artificial tears, antibiotics if needed
- Keratitis (inflammation of cornea): artificial tears, lubricants, or CS drops, antibiotics
- Uveitis (inflammation of various portions of the eye): CS drops, beta blockers, alpha antagonists, mydriatic ophthalmic drops
- Other ocular adverse events: follow

- Retinal vein occlusion (vascular event leading to vision changes, macular edema, glaucoma): anti-VEGF and steroid injection in addition to drug discontinuation
- Serous retinal detachment (fluid accumulation under layers of retina): drug hold/dose reduction/discontinuation
- Photophobia (oversensitivity to light): sunglasses, dim lights
- Keratitis (inflammation of cornea): artificial tears, lubricants, or CS drops, antibiotics
- Serous retinal detachment (fluid accumulation under layers of retina): drug hold/dose reduction/discontinuation

Identify and closely monitor at-risk patients (including those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration)

Advise patients to promptly report any changes in vision or any eye symptoms (and anticipate treatment hold pending further evaluation)

- Refers for baseline ophthalmic examination before beginning therapy (ophthalmologist should be made aware that patient is to start combination therapy)

- Is the patient diabetic?
- Does the patient wear contact lenses?
- Is there lid or periocular edema?
- Is the patient sensitive to light?
- Any recent eye injury, new medications, or exposure to toxic chemicals?
- When did symptoms start?
- Does the patient look jaundiced?
- Does the patient look unwell (or ill)?
- Promote good hand hygiene
- Encourage use of sunglasses and reduction in sun exposure
- Smoking cessation, control of comorbidities
- Diet (potentially including dietary supplements containing omega-3 and omega-6 fatty acids for dry eye syndrome)
- Identify and closely monitor at-risk patients (including those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration)
- Advise patients to promptly report any changes in vision or any eye symptoms (and anticipate treatment hold pending further evaluation)
- In general, anticipate referral to ophthalmology

Grading Toxicity

Grading T
- Is the patient diabetic?
- Does the patient wear contact lenses?
- Is there lid or periocular edema?
- Is the patient sensitive to light?
- Any recent eye injury, new medications, or exposure to toxic chemicals?
- When did symptoms start?
- Does the patient look jaundiced?
- Does the patient look unwell (or ill)?
Concern for permanent loss of vision: gradual or sudden visual loss
- Patient is unable to perform regular ADLs because of ocular issues
- Sudden vision disturbances such as photosensitivity, eye pain, and redness

**RED FLAGS:**
- Obtain ophthalmology clearance prior to restarting therapy
- Obtain ophthalmology clearance prior to restarting therapy
- Anticipate drug holds/dose modifications of targeted therapy for other moderate ocular toxicities, per prescribing information
- Anticipate permanent discontinuation of targeted therapy for other severe ocular toxicities, per prescribing information
- Reduce dose or discontinue if no improvement after 3 weeks
- Retinal pigment epithelial detachment: hold trametinib; reduce dose or discontinue if no improvement after 3 weeks
- Retinal vein occlusion: permanently discontinue trametinib and cobimetinib based on grade
- Other ocular adverse events: follow until visual symptoms improve or resolve with caution; MEKi can be continued; hold BRAF therapy
- Serous retinopathy: withhold MEKi until visual symptoms resolve; MEKi can be continued; hold BRAF therapy
- Uveitis (severe): hold dabrafenib, permanently discontinue
- Uveitis (persistent Grade 2 or >6 weeks duration): hold dabrafenib, permanently discontinue
- Uveitis (Grade 3 or 4): hold dabrafenib, permanently discontinue
- Antibiotics
- Antihistamines
- Cool compresses
- Artificial tears
- Other treatment-related symptoms
- If contact lenses are worn, advise patients to be meticulous about eye hydration, lens hygiene, and not using lenses beyond their disposal time
- In patients with diabetes, promote good control of blood glucose since it reduces risk of retinal disease
- Smoking cessation, control of comorbidities
- Support adherence to eye drops/topical therapy
- Follow-up exam if patients develop symptoms
- Refer for baseline ophthalmic examination before beginning therapy
- Overall Strategy:
  - Specific Ocular Issues:
    - Conjunctivitis (inflammation of the interior eyelids): antihistamines, CS, cool compresses, artificial tears, antibiotics if needed
    - Uveitis (inflammation of various portions of the eye): CS drops, beta blockers, alpha antagonists, mydriatic ophthalmic drops
    - Serous retinal detachment (fluid accumulation under layers of retina): drug hold/dose reduction/discontinuation
    - Retinal vein occlusion (vascular event leading to vision changes, macular edema, glaucoma): anti-VEGF and steroid injection in addition to drug discontinuation
    - Blindness (20/200 or worse) in affected eye(s)
    - Grade 4 (Highly symptomatic; pain, irritation, threatening)
    - Grade 3 (Severe)
    - Grade 2 (Moderate)
    - Grade 1 (Mild)
  - Management
    - Ocular photophobia, decreased visual acuity (worse than 20/40) in affected eye(s); limiting instrumental ADLs
    - Photosensitivity, etc.; marked decrease in visual acuity falls to 20/40 or better in affected eye(s); vision limitations affect QOL
    - High output (malignant hypertension, renal failure, severe glaucoma)
    - Grade 3 or 4 (Severe)
  - Specific targeted therapy dose modifications
  - Urgent referral to ophthalmology (within 24 hours)
Recognize:

- New or worsening symptoms (e.g., SOB, DOE, palpitations, fatigue, etc.)
- Changes in cardiac function, EF, symptoms, or lab values
- Changes in ECG, electrolytes, etc.
- Recognition of specific toxicity and revised grade

Assess other changes in oxygen saturation, BP, lung function

- Elevations in cardiac enzymes (e.g., troponin, CK)
- Changes in cardiac function: EF, symptoms, decreased EF
- Changes in symptoms on ACL exercise stress test
- DOE, SOB, palpitations, edema, etc.
- Other relevant symptoms (e.g., hypoxia, nausea, chest pain)

Care Step Pathway - Cardiotoxicity

Nursing Assessment

Heart Failure (left ventricular): A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements.

Grading Toxicity

Cardiotoxicity

Prior radiation therapy?

What exacerbates or improves symptoms?

Any underlying cardiac disease (CAD, Ill. of other?)

Any new presentation of TCM, IVF, etc.

What exacerbates or improves symptoms?

DiGeorge or Noonan?

Changes in BP?

Palpitations?

Leg edema?

SOB or DOE?

Change in mental level?

Listen for new and worsening symptoms:

Look:

- Is there leg edema?
- SOB or dyspneic distress?
- Palpitations?
- Leg edema?
- DOE or DOE?
Cardiotoxicity

**Management**

- Seek immediate care in emergency department for chest pain/pressure to evaluate for MI.
- Anticipate prompt evaluation of current cardiac symptoms by oncologist or cardiologist if there are nonurgent cardiac concerns.
- Assess cardiac function: lipid profile, ECG, ECHO/MUGA, stress test, BNP, cardiac enzymes.
- Baseline and below the institution’s LLN.
- For QTc >500 ms, permanently discontinued.
- Increases ≥20% from baseline.
- MEK inhibitors (cobimetinib and trametinib) to be discontinued if QTc remains >500 ms and below the institution’s LLN.
- For persistent LVEF value decreased >10% from baseline and below the institution’s LLN.
- Cardiology referral if condition worsens.
- Grades 3-4 (Severe or Life-threatening).
- Anticipate cardiology referral.

**Overall Strategy:**

- Review concomitant treatments that may affect heart function, particularly the QTc interval.
- Determine specific toxicity and related grade (if applicable).
- Review concomitant medications that may affect heart function, particularly the QTc interval.
- Monitoring cardiac function and medication.
- Encourage evaluation of lipid panel to assess cardiovascular risk.
- Avoid alcohol intake or psychoactive substances.
- Smoking cessation, control of comorbidities, stress reduction, weight control, exercise.
- Anticipate prompt evaluation of current cardiac symptoms by oncologist or cardiologist.
- Close cardiac follow up: CXR, ECHO/MUGA, CBC, CMP, BNP, C-reactive protein, CXR.
- Encourage evaluation of lipid panel to assess cardiovascular risk.
- Full cardiac workup at baseline: ECG (for vemurafenib), ECHO/MUGA (for any MEK-containing regimen), cardiac enzymes, CBC, CMP, BNP, C-reactive protein, CXR. Do not start MEK.
- Review concomitant medications that may affect heart function, particularly the QTc interval.
- Asymptomatic with laboratory or cardiac imaging abnormalities.
- Severe with symptoms at rest or on exertion (Death).
- Grade 1 (Mild).
- Grade 2 (Moderate).
- Grade 3 (Severe).
- Grade 4 (Potentially Life Threatening).
- Grade 5 (Life Threatening).
APPENDIX 2
### Detection and management of AEs and laboratory abnormalities not included in care step pathways for cobimetinib/vemurafenib

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Common symptoms</th>
<th>Common management/anticipatory guidance*</th>
</tr>
</thead>
</table>
| Arthralgias/myalgias                  | Joint pain swelling, or stiffness, feeling tired          | • Query patients regarding joint symptoms; standard supportive care (analgesia and anti-inflammatory drugs)  
• Anticipate treatment hold for intolerable Grade 2 (moderate pain, limiting instrumental ADLs) or Grade 3 (severe pain and self-care ADL limitations) |
| Chills                               | Shaking feeling/cold in absence of fever                  | • Query about symptoms, including symptoms related to serious febrile reactions  
• Anticipate treatment hold for intolerable Grade 2 (moderate tremors) or Grade 3 (severe or prolonged chills that are not responsive to narcotics) |
| Constipation/abdominal pain          | Infrequent stools/difficulty stooling, abdominal pain     | • Increase fluid; fiber; laxatives. Consider appropriate testing to evaluate bowel obstruction  
• Anticipate treatment hold for intolerable Grade 2 (persistent symptoms of constipation or moderate pain limiting instrumental ADLs) or Grade 3/4 (obstipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences) |
| Edema                                | Swelling of limbs, etc                                     | • Anticipate treatment hold for intolerable Grade 2 (moderate swelling, limiting instrumental ADLs) or Grade 3 (severe swelling, gross deviation from anatomic contour) |
| Embryo-Fetal Toxicity                | —                                                          | • Cobimetinib and vemurafenib can cause fetal harm. Females and males of child-bearing potential should use effective birth control during cobimetinib/vemurafenib treatment and for 2 weeks after the final dose of cobimetinib or vemurafenib (whichever is taken later) |
| Fatigue                              | Unrelenting exhaustion not relieved by rest               | • Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematological and biochemical abnormalities; standard supportive care  
• Anticipate treatment hold for fatigue not relieved by rest and limiting ADLs (Grade 2/3) |
| 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 evaluations for hypertension  
• Anticipate treatment hold for intolerable Grade 2 (moderate pain) or Grade 3 (severe pain, limiting self-care ADLs) |
| 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  
• Anticipate treatment hold for intolerable Grade 2 (moderate bleeding) or Grade 3/4 (severe bleeding requiring transfusion or radiologic, endoscopic, or operative intervention or life-threatening consequences) |
### Detection and management of AEs and laboratory abnormalities not included in care step pathways for cobimetinib/vemurafenib

(Continued)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Common symptoms</th>
<th>Common management/anticipatory guidance*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatotoxicity</strong></td>
<td>Abdominal pain or swelling; yellowing of skin or eyes; dark urine; easy bruising, loss of appetite; feeling tired or weak</td>
<td>• Monitor LFTs at baseline and monthly during treatment or as clinically indicated&lt;br&gt;• Anticipate treatment hold of cobimetinib at first occurrence of Grade 4 (&gt;20× upper limit of normal [ULN] for transaminases and alkaline phosphatase; &gt;10× ULN for bilirubin) and permanent discontinuation if not improved within 4 weeks&lt;br&gt;• Anticipate treatment hold of vemurafenib for intolerable Grade 2 (transaminases &gt;3× ULN, alkaline phosphatase &gt;2.5× ULN, or bilirubin &gt;1.5× ULN) or Grade 3/4 (transaminases or alkaline phosphatase &gt;5× ULN, bilirubin &gt;3× ULN) and permanent discontinuation if no recovery to Grade 0–1 or recurrent Grade 4 event</td>
</tr>
<tr>
<td><strong>Hypersensitivity reaction</strong></td>
<td>Swelling, feeling faint, rash, erythema, anaphylaxis</td>
<td>• Possible hospitalization&lt;br&gt;• Anticipate immediate permanent discontinuation of vemurafenib for patients with severe hypersensitivity reactions</td>
</tr>
<tr>
<td><strong>Nausea/vomiting</strong></td>
<td>Vomiting, queasiness, RUQ or LUQ pain</td>
<td>• May indicate hepatotoxicity; check LFTs/lipase/amylase; provide standard supportive care&lt;br&gt;• Anticipate treatment hold for intolerable Grade 2 (oral intake decreased or 3–5 vomiting episodes in 24 hours) or Grade 3/4 (inadequate oral intake or ≥6 vomiting episodes in 24 hours or life-threatening consequences)</td>
</tr>
<tr>
<td><strong>Radiation sensitization/recall</strong></td>
<td>Inflammatory skin reaction in areas treated with radiation</td>
<td>• Use vemurafenib with caution in patients with prior or ongoing radiotherapy or those who will be candidates for this treatment; advise patients to report if they have received radiation therapy or are planning to receive therapy</td>
</tr>
<tr>
<td><strong>Renal toxicity</strong></td>
<td>Decreased urine, blood in urine, swelling of ankles, decrease in appetite</td>
<td>• Measure serum creatinine before treatment initiation and periodically during treatment; monitor kidney function&lt;br&gt;• Anticipate treatment hold with intolerable Grade 2 (eGFR or CrCl 59 to 30 mL/min/1.73 m²) or Grade 3/4 (eGFR or CrCl ≤29 mL/min/1.73 m²)</td>
</tr>
</tbody>
</table>

*When treatment holds are required, resume therapy at a lower dose level following improvement to Grade 0 to 1. Permanently discontinue targeted therapies in case of persistent intolerable Grade 2 events, persistent Grade 3 events, and persistent or recurrent Grade 4 events unless otherwise specified.