AIM AT MELANOMA FOUNDATION | MELANOMA NURSING INITIATIVE

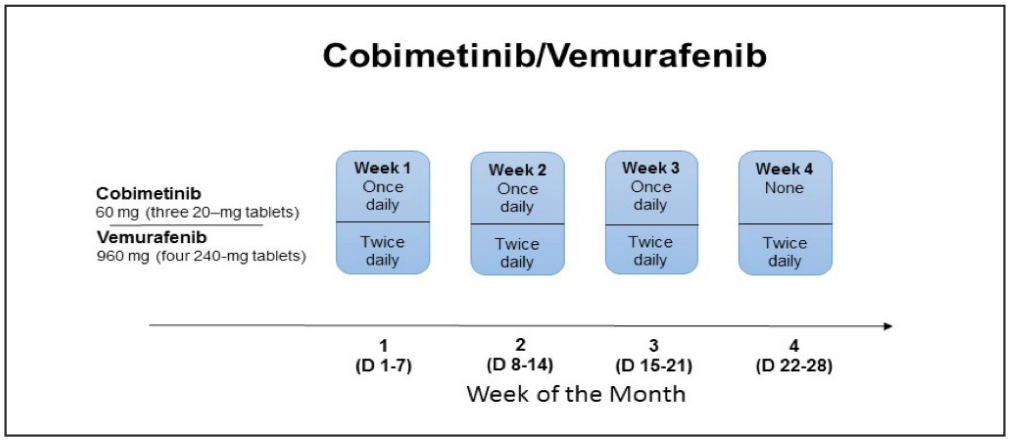
Cobimetinib/Vemurafenib Combination Therapy for Melanoma: A Nursing Tool From The Melanoma Nursing Initiative (MNI)

Cobimetinib (Cotellic®)/vemurafenib (Zelboraf®) 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 inhibitor 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.

DRUG-DOSING/ADMINISTRATION

- 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 a total daily dosage of 1920 mg, each according to the regimens outlined below. The cobimetinib dose can be taken at the same time as one of the vemurafenib doses. The schedule repeats until disease progression or unacceptable toxicity occurs.



- 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 missed dose can be taken up to 4 hours prior to next dose
  - A double dose of either cobimetinib or vemurafenib should NOT be taken to make up for a missed dose
- Cobimetinib and vemurafenib may be administered with or without food. Vemurafenib tablets should not be crushed or chewed
- In general, strong or moderate CYP3A4 inhibitors should be avoided while taking cobimetinib. If short-term concomitant use of a moderate CYP3A4 inhibitor is unavoidable, ***reduce*** the cobimetinib dose from 60 to 20 mg. After discontinuation of the CYP3A4 inhibitor, resume previous dose of cobimetinib 60 mg
- In general, strong CYP3A4 inducers should be avoided while taking vemurafenib. If concomitant use of a strong CYP3A4 inducer is unavoidable, increase the vemurafenib dose by 240 mg (one tablet). After discontinuation of the CYP3A4 inducer for 2 weeks, resume the vemurafenib dose taken before initiating the strong CYP3A4 inducer

SIDE EFFECTS AND THEIR MANAGEMENT

- 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

irAE category	Examples	Treatment guidance (Appendix number)
Most common	Fever/pyrexia	1
	Chills	2
	Edema	2
	Headache	2
	Gastrointestinal	2
	- Diarrhea	
	- Nausea & vomiting	
	- Constipation/abdominal pain	
	Skin toxicities (rash/photosensitivity)	1 & 2
	Joint/muscle pain (arthralgias/myalgias)	2
	Fatigue/tiredness	2
Less common but serious	New primary cancers	1
	- Cutaneous (eg, basal cell or squamous cell carcinoma, keratocanthoma, new melanoma)	
	- Non-cutaneous	
	Ocular toxicity	1
	Cardiovascular	
	- Cardiomyopathy (↓ LVEF)	1
	- Hemorrhage	2
	- Venous thromboembolism (pulmonary embolism, deep vein thrombosis)	2
	- Hemolytic anemia	2
	Colitis and gastrointestinal perforation	2
	Interstitial lung disease/pneumonitis	2
	Renal toxicity	2

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

Cobimetinib	**Dose Reduction From 60 mg Orally Once Daily To**
First dose reduction Second dose reduction Subsequent modification	40 mg orally once daily 20 mg orally once daily Permanently discontinue if unable to tolerate 20 mg once daily
Vemurafenib	**Dose Reduction From 960 mg Orally Twice Daily To**
First dose reduction Second dose reduction Subsequent modification	720 mg orally twice daily 480 mg orally twice daily Permanently discontinue if unable to tolerate 480 mg twice daily

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 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

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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, 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.

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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
https://www.cancer.org/cancer/melanoma-skin-cancer/treating/targeted-therapy.html

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ADDITIONAL RESOURCES

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- 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
- Mavropoulos JC, Wang TS. Managing the skin toxicities from new melanoma drugs. *Curr Treat Options Oncol*. 2014;15:218-301.
- My Cotellic + Zelboraf Treatment Guide. South San Francisco, CA: Genentech, Inc.; 2016. Available at: https://www.cotellic.com/content/dam/gene/cotellic/patient/PDFs/Patient_Treatment_Guide_Website_Resource.pdf. Accessed August 10, 2017.
- Rubin KM. Care and management of unique toxicities associated with MAPK pathway-targeted therapies in patients with advanced melanoma. *Clin J Oncol Nurs*. In press.
- Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol*. 2015;7:122-136.
- Zelboraf® [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2017. Available at: https://www.gene.com/download/pdf/zelboraf_prescribing.pdf.

Click here for downloadable action plans to customize for your patients

APPENDIX 1

Care Step Pathway - Pyrexia
(elevated body temperature in the absence of clinical or microbiological evidence of infection)

Nursing Assessment

Look:
- Does the patient appear unwell?
  - Diaphoretic?
  - Pale?
- Does the patient appear dehydrated?
- Is the patient currently febrile?
- If febrile, are rigors present?

Listen:
- Onset and duration of fevers
- Associated symptoms (chills, rigors, decreased urine output, hypotension, malaise, fatigue, GI or respiratory symptoms)
- Method of temperature assessment (oral, axillary, temporal)
- Self-management of fevers (OTC agents, medications, tepid baths)
- Adequacy of fluid intake in the last 24 hours (how much, types, etc)
- How the patient has been taking BRAF/MEKi medications
- Potential infectious causes
  - Symptoms suggestive of infectious etiology (e.g., upper respiratory, urinary)
  - Recent sick contacts?
  - Recent exposure to animals?
  - Recent international or national travel?

Recognize:
- Other treatment-related adverse events
- Grade of fever and chills if present
- Other symptoms, such as dehydration, rigors, hypotension (complex pyrexia syndrome)
- Potential infectious causes (via urinalysis, urine culture, throat cultures, blood cultures, etc)
- Impact of symptoms on QOL/performance status

Grading Toxicity

Grade 1 (Mild)
Asymptomatic; mild, low-grade fevers (99.0°F–101.2°F [37.2°C–38.4°C])

Grade 2 (Moderate)
Fevers (101.3°F–104.0°F [38.5°C–40.0°C]); mildly symptomatic (chills, etc) affecting ADLs

Grade 3 (Severe)
Any fever >104.0°F (>40.0°C) *or* fever of 101.3°F–104.0°F (38.5°C–40.0°C) that is moderately symptomatic (rigors, chills, decreased urinary output, hypotension); limiting self-care ADLs

Grade 4 (Potentially Life-Threatening)
Any fever >101.3°F (38.5°C) that is **highly** symptomatic (acute renal insufficiency, hypotension requiring hospitalization, prompt supportive care)

Grade 5 (Death)

Management

Grade 1 (Mild)

- Acetaminophen or ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours
  - Monitor renal and hepatic function during antipyretic treatment
  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen
- Increase oral hydration to minimize insensible losses. Suggested fluids: water, juice, sports drinks (e.g., Gatorade®, Powerade®, Pedialyte®)
- Review medication profile with patient and family, including prescriptions, OTCs, herbals, supplements, or other complementary therapies
  - Determine if concomitant medications contain antipyretics
  - Assess for potential drug-drug interactions
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

Grade 2 (Moderate)

- For temperatures >101.3°F (38.5°C), dabrafenib to be held/trametinib to be continued
- Acetaminophen or ibuprofen q4-6 hrs until fever resolves (<99°F [37.2°C]) for at least 24 hours
  - Monitor renal and hepatic function during antipyretic treatment
  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen
- Institute re-hydration strategies, particularly if patient is hypotensive or there is other clinical concern. Set hydration goals
  - Oral, advise fluids: water, rehydration drinks (Pedialyte), juice, sports drinks (Gatorade, Powerade), popsicles
  - Intravenous, as needed
- 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 (eg, switch from dabrafenib to vemurafenib if fever persists and refractory to antipyretics or prednisone treatment, causing moderate changes in the patient's ADLs)
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence
- Upon symptom and fever resolution (<99°F [37.2°C]) for 24 hours, possible treatment restart with appropriate dose reduction
- 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)

Grades 3-4 (Severe or Potentially Life-Threatening)

- For fevers >104°F (>40.0°C), or any fever accompanied by chills, hypotension, dehydration, or renal failure, **both** dabrafenib and trametinib will be held
- For intolerable temperatures 102.3°F–104.0°F (39.1°C– 40.0°C) and all temperatures >104°F (40.0°C), both vemurafenib and cobimetinib will be held
- Targeted therapy will be held (Grade 3) or discontinued (Grade 4)
- Prompt medical and supportive care interventions
  - Hospitalization, if clinically indicated
- Acetaminophen or ibuprofen q4-6 hrs until fever resolves (<99°F; 37.2°C) for at least 24 hours
  - Monitor renal and hepatic function during antipyretic treatment
  - Do not exceed 4000 mg/d acetaminophen or 3200 mg/d ibuprofen
- Aggressive hydration management to address hypotension, etc
- 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., dabrafenib to vemurafenib)
- Grade 3: Upon symptom and fever resolution for (<99°F [37.2°C]) for 24 hours, possible treatment restart
  - Same agents with appropriate dose reductions
  - Oral corticosteroid premedication (10 mg/d) to be used for second or subsequent pyrexia with dabrafenib if prolonged (>3 days) or with complications
- Change to different targeted therapy regimen, if clinically appropriate (e.g., switch from dabrafenib to vemurafenib if fever persists)
- Assess patient & family understanding of recommendations and rationale
- Identify barriers to adherence

ADL = activities of daily living; CS = corticosteroid; GI = gastrointestinal; OTC = over the counter; QOL = quality of life

Care Step Pathway - Skin Toxicities

Nursing Assessment

Look:
- Does the patient appear uncomfortable?
- Does the patient appear unwell?
- Is there obvious rash?
- Suspicious skin lesion(s)?
- Xerosis? Is the patient scratching during the visit?
- Skin changes/new lesion(s): photosensitivity reactions, sunburn, or other cutaneous lesions suspicious for actinic keratoses, keratoacanthomas, cutaneous squamous cell carcinomas, or new melanomas?

Listen:
- Rash and/or pruritus?
- Other cutaneous symptoms: (eg, photosensivity)?
- Are symptoms interfering with ADLs? With sleep?
- Have symptoms worsened?
- What interventions has patient tried (if any): effective and ineffective?
- Question patient and family regarding history of skin problems in the past (i.e., sun damage, dermatitis [with prior immunoRx], wounds, underlying skin disorders [e.g., psoriasis, eczema])
- Any exposure to new chemicals, soaps, or allergens (animals, travels)?

Recognize:
- Is there a personal or family history of dermatitis, pre-existing skin issues (psoriasis, skin cancer, wounds)?
- Is there evidence of scratching, such as abrasions?
- Is skin intact?
- Are there skin changes?
  - Xerosis
  - Changes in skin pigment or color
- Oral involvement?
- Perform comprehensive skin examination and determine grade of toxicity
- What impact have the symptoms had on QOL?
- Relevant social history (occupational, environmental, leisure-type activities)

Grading Toxicity

RASH (maculopapular rash, acneiform rash, or dermatitis)

Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Maculopapular rash frequently affects the upper trunk, spreading centripetally and associated with pruritus, whereas acneiform rash typically appears on the face, scalp, upper chest, and back.

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADLs	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADLs; skin sloughing covering <10% BSA	Papules/pustules covering any % BSA, with or without symptoms and associated with superinfection requiring IV antibiotics; skin sloughing covering 10-30% BSA	

PRURITUS

Definition: A disorder characterized by an intense itching sensation.

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADLs	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated		

Management

Overall Strategy:

- Introduce concept of treatment interruption and possible dose reduction when educating patients prior to initiation of therapy
- Refer for baseline skin examination before beginning therapy and closely monitor at-risk patients
- Assess for other etiology of rash: ask patient about new medications, herbals, supplements, alternative/complementary therapies
- Encourage patients to report any skin changes promptly

Intervention (at-risk patients)

Gentle skin care:

- Avoid soap. Instead, use non-soap cleansers (mild, fragrance- & dye-free soap on the axillae, genitalia, and feet)
- Avoid hot baths
- Avoid tight clothing/shoes
- Keep fingernails short (to avoid scratching)
- Daily applications of nonsteroidal moisturizers or emollients containing humectants (urea, glycerin)
- Apply moisturizers and emollients in the direction of hair growth to minimize development of folliculitis

Advise sun protective measures:

- Use of UV-protective clothing, sunglasses, sunscreen against UVA rays or broad spectrum (UVA/UVB), avoidance of direct and indirect sunlight
- Assess patient and family understanding of prevention strategies and rationale
- Identify barriers to adherence

Grade 1 (Mild)

- Observation only
- Emollients
- Sun avoidance/sunscreen
- Possible use of topical antihistamines

Patient Counseling:

- Emollients twice daily
- Antihistamines and analgesics, if applicable
- Strict UV protection w/ SPF 30 sunscreen/eye protection
- Gentle exfoliation for follicular rash
- Treatment w/ low-potency topical steroids to be started/ possible treatment interruption for persistent or worsening adverse events

Grade 2 (Moderate)

- Antihistamines and analgesics as needed
- Topical steroids and/or antipruritics (topical/oral) to be started
- Persistent Grade 2: therapy to be held until Grade 0-1
  - Start oral steroid, taper no longer than 7 days
- Rash: consider topical antibiotic (clindamycin gel) if indicated
- Consider referral to dermatologist

Patient Counseling:

- Anticipate treatment with higher-potency topical or oral steroids
- Consider referral to dermatologist or provider trained in managing toxicities from targeted therapy

Grade 3 (Severe)

- Treatment to be held until <Grade 1; resume at a lower dose
- Oral steroid to be started, taper no longer than 7 days
- Rash: consider topical antibiotic
- Refer to dermatologist

Patient Counseling:

- Anticipatory guidance regarding hospitalization for systemic steroids and/or hydration

Grade 4 (Potentially Life-Threatening)

- Targeted therapy to be permanently discontinued
- Consider hospitalization for IV hydration, steroids, IV antibiotics, electrolyte replacement

Patient Counseling:

- Anticipatory guidance regarding treatment discontinuation or possible hospitalization for steroids and/or hydration
- Referral to dermatologist

RED FLAGS:

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

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

Care Step Pathway - Ocular Toxicity

Nursing Assessment

Look:
- Does the patient look unwell (or ill)?
- Does the patient look uncomfortable?
- Does the patient look jaundiced?
- Is there any eye redness? Drainage? Tearing?
- Are pupils reactive?
- Is the patient sensitive to light?
- Is there lid or periocular edema?
- Are there skin lesions surrounding the eye(s)?

Listen:
- Patient and family descriptions of current ocular health and any eye problems, both current and in the past (e.g., glaucoma, retinal issues, eye inflammation)
- Reports of specific eye complaints: redness, watering, drainage, change in acuity, diplopia, floaters, photophobia?
- When did symptoms start?
- Any recent eye injury, new medications, or exposure to toxic chemicals?
- Does the patient wear contact lenses?
- Is the patient diabetic?
- Associated symptoms: headache, vomiting, nausea?

Recognize:
- Patients at risk
- The specific ocular complaint (if possible) and determine grade
- Other treatment-related symptoms
- How vision limitations affect QOL
- Need for urgent evaluation (if indicated)

Grading Toxicity (Overall, Ocular Toxicity)

Grade 1 (Mild)
Asymptomatic; clinical or diagnostic observations only

Grade 2 (Moderate)
Symptomatic (pain, irritation, photosensitivity, etc.); visual acuity falls to 20/40 or better in affected eye(s); limiting instrumental ADLs

Grade 3 (Severe)
Highly symptomatic (pain, irritation, photosensitivity, etc), marked decrease in visual acuity (worse than 20/40) in affected eye(s); limiting self-care ADLs

Grade 4 (potentially life-threatening)
Blindness (20/200 or worse) in affected eye(s)

Management

Overall Strategy:

- Refer for baseline ophthalmic examination before beginning therapy (ophthalmologist should be made aware that patient is to start combination therapy)
- Follow-up exam if patients develop symptoms
- Advise patients to promptly report any changes in vision or any eye symptoms (and anticipate treatment hold pending further evaluation)
- Identify and closely monitor at-risk patients (including those with a history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration)
- Promote healthy lifestyle:
  - Diet (potentially including dietary supplements containing omega-3 and omega-6 fatty acids for dry eye syndrome)
  - Smoking cessation, control of comorbidities
  - Encourage use of sunglasses and reduction in sun exposure
  - Promote good hand hygiene
  - In patients with diabetes, promote good control of blood glucose since it reduces risk of retinal disease
- If contact lenses are worn, advise patients to be meticulous about eye hydration, lens hygiene, and not using lenses beyond their disposal time

Specific Ocular Issues:

- When ocular issues are identified, anticipate management by the treating ophthalmologist (and provide anticipatory guidance/assistance, as appropriate):
  - 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
  - Conjunctivitis (inflammation of the interior eyelids): antihistamines, CS, cool compresses, artificial tears, antibiotics if needed
  - Photophobia (oversensitivity to light): sunglasses, dim lights
  - 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
  - Retinal pigment epithelial detachment (bilateral or multifocal separation of the retina from back of eye, leading to sudden vision changes): drug hold/dose reduction/discontinuation

Grade 1 (Mild)

- In general, anticipate referral to ophthalmology
- Specific targeted therapy dose modifications:
  - Uveitis: BRAFi may be continued with caution; MEKi can be continued; obtain prompt visit with ophthalmologist
  - Other ocular adverse events: follow standard dose modifications/holds based on grade
- Support adherence to eye drops/topical therapy

Grade 2 (Moderate)

- Urgent referral to ophthalmology (within 24 hours)
- Specific targeted therapy dose modifications/holds/discontinuations:
  - Uveitis (persistent Grade 2 or >6 weeks duration): hold BRAFi therapy
  - Serous retinopathy: withhold MEKi until visual symptoms improve. Use dose reduction scheme based on severity
  - Retinal vein occlusion: permanently discontinue trametinib and cobimetinib
- Retinal pigment epithelial detachment: hold trametinib; reduce dose or discontinue if no improvement after 3 weeks. Assess adherence to eye drops/topical therapy
- Anticipate drug holds/dose modifications of targeted therapy for other moderate ocular toxicities, per prescribing information
- Obtain ophthalmology clearance prior to restarting therapy

Grades 3 or 4 (Severe)

- Urgent referral to ophthalmology (within 24 hours)
- Specific targeted therapy drug modifications/holds/discontinuations:
  - Uveitis (severe): hold dabrafenib, permanently discontinue if no improvement within 6 weeks
  - Serous retinopathy: withhold MEKi until visual symptoms improve. Use dose reduction scheme based on severity
  - Retinal vein occlusion: permanently discontinue trametinib and cobimetinib
  - Retinal pigment epithelial detachment: hold trametinib; reduce dose or discontinue if no improvement after 3 weeks
  - Anticipate permanent discontinuation of targeted therapy for other severe ocular toxicities, per prescribing information
  - Assess adherence to eye drops/topical therapy
  - Obtain ophthalmology clearance prior to restarting therapy

RED FLAGS:

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

ADLs = activities of daily living; CS = corticosteroids; QOL = quality of life

Care Step Pathway - Cardiotoxicity

Nursing Assessment

Look:
- Does the patient look unwell?
- Fatigued?
- Diaphoretic?
- SOB or in respiratory distress?
- Is there leg edema?

Listen for new and worsening symptoms:
- Change in energy level?
- SOB or DOE?
- Leg edema?
- Palpitations?
- Changes in BP?
- Dizziness or syncope?
- What exacerbates or improves symptoms?
- Any new prescribed or OTC meds? Illicit substances?
- Any underlying cardiac disease (CAD, MI, or other)?
- What exacerbates or improves symptoms?
- Prior radiation therapy?

Recognize:
- Determine specific toxicity and related grade (if applicable)
- Other related symptoms: hypotension, syncope, chest pain, DOE, SOB, palpitations, edema, etc.
- Impact of symptoms on QOL performance status
- Changes in cardiac function: ECG changes, decreased EF, elevated cardiac enzymes (troponin, CK)
- Assess other changes in oxygen saturation, BP, lung function

Grading Toxicity

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.

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
Asymptomatic with laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal exertion (intervention needed)	Life threatening consequences (urgent intervention required)	

QTc interval prolongation: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.

Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)	Grade 5 (Death)
QTc 450–480 ms	QTc 481–500 ms	QTc ≥501 ms on at least 2 separate ECGs	QTc ≥501 or >60 ms change from baseline *and* torsade de pointes, polymorphic ventricular tachycardia, or signs or symptoms of serious arrhythmia	

Management

Overall Strategy:

- Review concomitant treatments that may affect heart function, particularly the QTc interval (e.g., fluoroquinolones, ondansetron, HIV antivirals)
- 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 MEKi therapy if QTc >500 ms
- Repeat ECHO for MEK-containing regimen at 1 month and every 2–3 months while on treatment. If ECG performed (on vemurafenib), repeat ECG at 14 days, monthly x3, and then every 2–3 months while on treatment, more frequently if on medications affecting QTc, or as needed if patient starts new agents that may prolong QT interval
- Prevention (no known strategies), but encourage healthy lifestyle
- Introduce concept of dose reduction or dose holding when educating patients prior to initiation of therapy
- Assess adherence with BP medications if patients are hypertensive

Grade 1 (Mild)

- Anticipate cardiology referral if condition worsens
- MEK inhibitors (cobimetinib and trametinib) to be held for a LVEF value decreased >10% from baseline and below the institution's LLN
- Promote adequate hydration and medication adherence
- Advise patients to avoid alcohol intake or other psychoactive substances
- Encourage evaluation of lipid panel to assess cardiovascular risk
- Promote healthy lifestyle
    - Smoking cessation, control of comorbidities, stress reduction, weight control, exercise

Grade 2 (Moderate)

- Anticipate cardiology referral
- Trametinib to be discontinued for symptomatic congestive heart failure or a LVEF value decreased ≥20% from baseline and below the institution's LLN
- Cobimetinib to be discontinued for a persistent LVEF value decrease >10% from baseline and below the institution's LLN *or* for persistent symptoms
- Dabrafenib to be held for a LVEF value decreased 20% from baseline and below the institution's LLN
- Anticipate prompt evaluation of current cardiac symptoms by oncologist or cardiologist if there are nonurgent cardiac symptoms
- Seek immediate care in emergency department for chest pain/pressure to evaluate for MI

Grades 3-4 (Severe or Life-threatening)

- Anticipate urgent cardiology referral
- For QTc >500 ms, vemurafenib to be held and permanently discontinued if QTc remains >500 ms and increased 60 ms from pretreatment (after controlling cardiac risk factors for QTc interval prolongation)
- For persistent LVEF decrease, targeted therapies to be permanently discontinued
- Assess cardiac function: lipid profile, ECG, ECHO/MUGA, stress test, BNP, cardiac enzymes
- Seek immediate care in emergency department for chest pain/pressure to evaluate for MI

BNP = brain natriuretic peptide; BP = blood pressure; CAD = coronary artery disease; CBC = complete blood count; CK = creatine kinase; CMP = complete metabolic panel; CXR = chest radiograph; DOE = dyspnea on exertion; ECG = electrocardiography; ECHO = echocardiography; EF = ejection fraction; GI = gastrointestinal; HIV = human immunodeficiency virus; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MUGA = multigated acquisition scan; OTC = over the counter; QOL = quality of life; SOB = short of breath.

APPENDIX 2

Detection and management of AEs and laboratory abnormalities not included in care step pathways for cobimetinib/vemurafenib

Adverse event	Common symptoms	Common management/anticipatory guidance*
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 (constipation 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)

Adverse event	Common symptoms	Common management/anticipatory guidance*
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 • Anticipate treatment hold of cobimetinib at first occurrence of Grade 4 (>20× upper limit of normal [ULN] for transaminases and alkaline phosphatase; >10× ULN for bilirubin) and permanent discontinuation if not improved within 4 weeks • Anticipate treatment hold of vemurafenib for intolerable Grade 2 (transaminases >3× ULN, alkaline phosphatase >2.5× ULN, or bilirubin >1.5× ULN) or Grade 3/4 (transaminases or alkaline phosphatase >5× ULN, bilirubin >3× ULN) and permanent discontinuation if no recovery to Grade 0–1 or recurrent Grade 4 event
Hypersensitivity reaction	Swelling, feeling faint, rash, erythema, anaphylaxis	• Possible hospitalization • Anticipate immediate permanent discontinuation of vemurafenib for patients with severe hypersensitivity reactions
Nausea/vomiting	Vomiting, queasiness, RUQ or LUQ pain	• May indicate hepatotoxicity; check LFTs/lipase/amylase; provide standard supportive care • 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)
Radiation sensitization/recall	Inflammatory skin reaction in areas treated with radiation	• 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
Renal toxicity	Decreased urine, blood in urine, swelling of ankles, decrease in appetite	• Measure serum creatinine before treatment initiation and periodically during treatment; monitor kidney function • Anticipate treatment hold with intolerable Grade 2 (eGFR or CrCl 59 to 30 mL/min/1.73 m^2) or Grade 3/4 (eGFR or CrCl ≤29 mL/min/1.73 m^2)

*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.